

METHYL N-PROPYL ETHER: A REPORT OF A CLINICAL TRIAL

W. D. KYLE, M.D.*

METHYL N-PROPYL ETHER was first described by Chancel in 1869, but its valuable anaesthetic properties were not appreciated until its inclusion in the long series of ethers tested by Krantz and his co-workers in the United States.

The clinical trials of methyl n-propyl ether following Krantz's original description of its anaesthetic properties and pharmacology in 1946 (1) showed that it might be superior to diethyl ether as an inhalation anaesthetic, in having the useful properties of diethyl ether in enhanced degree without some of its undesirable features.

Many further reports have stressed the advantages of methyl n-propyl ether over diethyl ether, and yet the agent has not gained any wide acceptance in clinical anaesthesia. It was in an attempt to determine the reasons for this lack of acceptance of this agent that the following study of methyl n-propyl ether was carried out.

CHEMISTRY AND PHARMACOLOGY

Methyl n-propyl ether is a colourless, highly inflammable, volatile liquid, with a characteristic ethereal odour. The physical and chemical properties of methyl n-propyl ether are in many ways similar to those of diethyl ether, as the two are isomeric. They may be summarized and compared as follows:

	<i>Methyl n-propyl ether</i>	<i>Diethyl ether</i>	<i>Ref</i>
Formula	CH ₃ -O-C ₃ H ₇	C ₂ H ₅ -O-C ₂ H ₅	
Description	volatile clear colourless liquids with characteristic odours		
S.G. at 15° C	0.731	0.720	
B.P. at 760 mm Hg	39° C	34.5° C	
Vapour press. at 28° C	520 mm Hg	597 mm Hg	(3)
Solubility in water (per 100 cc. at 25° C.)	5.0 ml	8.6 ml	
Oil/water coefficient	10 plus or minus 1	4 plus or minus 0.4	(2, 3)

Krantz and his co-workers (1, 3, 5) subjected this substance to extensive experiments on rats, dogs, and *Macacus Rhesus* monkeys. Their findings may be summarized as follows:

1. Methyl n-propyl ether produced no significant histological change in the livers of animals and did not interfere with hepatic function as demonstrated in the bromsulphalein test (1).

2. It produced no pathological changes in the kidney nor alterations in the urine (3).

3. It produced no significant changes in CO₂ combining power, urea nitrogen, or clotting time of the blood (1).

*University Hospital, Edmonton, Alberta.

4. It caused no abnormalities in ECG tracings, pulse, or blood pressure (1, 6).

5. In the dog, it is approximately 25 per cent more potent than diethyl ether. Its anaesthetic index (ml/kg required for respiratory arrest)/(ml/kg required for surgical anaesthesia) was 2.5, compared to 2.1 for diethyl ether, and 1.6 for chloroform (1, 6).

6 Prolonged anaesthesia in dog and monkey did not give rise to detectable methyl alcohol or formaldehyde in the blood, indicating that, like diethyl ether, methyl n-propyl ether is not metabolized in the body (3).

PREVIOUS CLINICAL TRIALS

In their series of cases White *et al* (6) found that, compared with diethyl ether, methyl n-propyl ether was less irritating to the respiratory tract, induction with it smoother, the pulse rate not as rapid, and muscular relaxation more easily achieved. Post-operative nausea and vomiting were less, and there were no pulmonary complications. They state that it might be used alone as an induction agent, and Rochberg (8) and Rees (12) state that if other induction agents are used, the change to methyl n-propyl ether is made more smoothly and easily than with diethyl ether. All writers agree that respiration under methyl n-propyl ether anaesthesia is quiet, unhurried, and moderately deep (6, 9, 12).

Although complaints are on record (7) by operating teams against its odour, it stands high on a list of anaesthetic agents arranged in order of decreasing pleasantness of odour (3).

Fisher and Whitacre (7) in 1947 concluded, in a series of over five hundred cases, that decreased irritation of the respiratory tract was the agent's only advantage over diethyl ether.

Shane (9) claimed that anaesthesia with methyl n-propyl ether gave better relaxation of the abdominal musculature and contraction of the intestines than that obtained with diethyl ether.

Redgate and Bannister (11) report a case in which overdose of the drug resulted in depression of the cardiovascular system, but Shane (9) states that in ordinary concentration it has no effect on cardiovascular function. Barnett (16) reported two cases of cardiovascular depression, but states they responded rapidly to lightening of the methyl n-propyl ether anaesthesia. Rochberg (8) reported the tendency to capillary oozing to be reduced.

Sykes (10) found the chief points of interest to be the lack of irritation of the respiratory tract and the small number of pulmonary and gastric complications.

Rochberg (8), Dawkins (13), and Kaplan (14) all reported a very short recovery period, which was generally pleasant. However Middleton and Picken (15) reported no significant alteration in the incidence of postoperative nausea and vomiting as compared with that found when using diethyl ether.

CLINICAL TRIAL

With these proposed advantages and disadvantages in mind the agent was used in a carefully documented series of over 150 cases.

Patients were unselected as regards age (which varied from sixteen months to seventy-seven years), operation proposed (which included all types of major and

minor surgery, including thoracic, cardiac and intracranial cases), or physical condition. Duration of anaesthesia varied from fifteen minutes to five hours and forty minutes.

The agent was used in all available methods and techniques, which included open and semi-drop, fractional rebreathing, non-rebreathing, semi-closed and closed circle absorber systems.

Preoperative medication was that routinely employed for other methods of general anaesthesia, and consisted of an opiate and a belladonna drug one hour before operation. In the case of children, atropine and rectal Pentothal® were used in most cases.

Induction

Induction was consistently smooth. The lack of irritation of the respiratory tract as demonstrated by the persistent absence of coughing, breath-holding, and spasm was a very marked feature of the agent.

Induction was generally rapid, except in those cases where methyl n-propyl ether alone was used by the open drop method. It does not vaporize as readily as diethyl ether, and as a result is slower in action, some other agent was therefore generally used in conjunction.

Maintenance

Methyl n-propyl ether was used with a wide variety of agents including divinyl ether, trichlorethylene, cyclopropane, nitrous oxide, and Pentothal®, as well as various muscle relaxants. The change from another agent to methyl n-propyl ether was found to be routinely smooth and much more rapidly accomplished than the change to diethyl ether might be expected to be.

Maintenance was consistently uneventful. Because of the low volatility of the agent it was found most effective in closed circle systems. A slow pulse was usually present, a fall in blood pressure was noted only with very deep anaesthesia, and this was never severe. Cardiac irregularities did not occur. The marked cardiovascular depression reported was not encountered.

Respiration was quiet and generally slow in contrast to the respiration noted with diethyl ether. Patients could be carried in light planes of anaesthesia without bucking or breath-holding.

The degree of muscle relaxation of both jaw and abdominal wall was felt to be markedly better than that obtained with comparable levels using diethyl ether. Intubations were accomplished with ease routinely under excellent relaxation. Quietness and constriction of the bowel were frequently commented upon, in some cases the surgeons compared the abdomen to that obtained only with spinal analgesia. In obstetrical cases the degree of relaxation was always satisfactory for intrauterine manipulations.

One technical complication arose owing to the fact that the patient's eyeball tends to rove at all levels of anaesthesia; therefore the agent was soon rejected for ophthalmological cases.

Recovery

The recovery time from methyl n-propyl ether anaesthesia was considered to be shorter than that which might be expected in comparable cases using diethyl

ether. Postoperative nausea and vomiting were never severe, and the incidence was about 15 per cent. Immediate or remote postoperative complications attributable to the agent did not occur in this series.

Unpleasant Odour

The references to the unpleasant odour of the agent were confirmed. Despite the fact that the patient breathes the agent without evidence of irritation, and recovers from its use without undue nausea and vomiting, the unpleasant odour soon led to its use being restricted to the closed circle system to prevent complaints of headache and other uncomplimentary comments from operating-room personnel

SUMMARY

This is a brief report on the use of methyl n-propyl ether in over one hundred and fifty unselected cases undergoing all types of surgery. The agent was used by all available techniques and methods.

Smooth induction or changeover from other agents was noted, with extremely little irritation of the respiratory tract. Maintenance was not difficult and was characterized by quiet respiration, a slow pulse, and consistently excellent muscle relaxation. Cardiovascular depression was not a problem in this series.

The main disadvantage of the agent is its disagreeable odour.

Methyl n-propyl ether appears to have some specific advantages over diethyl ether, and thus deserves a definite but limited place in the practice of anaesthesia.

RÉSUMÉ

L'auteur expose brièvement les constatations qu'il a fait en utilisant l'éther méthyle N-propyle dans plus de cent cinquante cas non choisis qui subirent différentes interventions chirurgicales. L'agent anesthésique fut employé avec toutes les techniques et méthodes disponibles.

Il fut noté que l'induction ou bien l'emploi après d'autres agents se faisaient sans difficulté et sans notable irritation du système respiratoire. L'anesthésie fut maintenue aisément et se caractérisa par, une respiration facile, un pouls lent et un excellent et constant relâchement musculaire. La dépression cardiovasculaire ne fut pas un problème dans cette série.

Le désavantage principal de cet agent est son odeur désagréable.

L'éther méthyle N-propyle semble avoir des avantages spécifiques sur l'éther diéthylique et c'est pourquoi il a une place définie mais limitée dans la pratique anesthésique.

REFERENCES

- 1 KRANTZ, J. C. Jr., EVANS, W. E. Jr., CARR, J. C. and KIBLER, D. V. *J. Pharmacol. & Exper. Therap.* 86: 138 (1946)
- 2 CARR, J. C., KIBLER, D. V. and KRANTZ, J. C. Jr. *Anesthesiology* 5: 495 (1944)
- 3 ——— *Anesthesiology* 8: 53 (1947).
- 4 KIBLER, D. V. *Anesthesiology* 8: 288 (1947)
- 5 KRANTZ, J. C. Jr., CARR, J. C., IWAMOTO, H. K. and SAUERWALD, M. J. *Anesthesiology* 8: 497 (1947)

6. WHITE, M. L. T., SHANE, S. M. and KRANTZ, J. C. Jr. *Anesthesiology* 7: 663 (1946).
- 7 FISHER, A J, WHITACRE, R J. *Anesthesiology* 8 156 (1947)
- 8 ROCHBERG, S. *Anesthesiology* 8 637 (1947)
9. SHANE, S. M. *Anesth & Analg* 26 260 (1947).
10. SYKES, C. E *Brit Med. J.*: 420 (1949)
11. REDGATE, J. W. and BANNISTER, A K. *Anaesthesia* 5 183 (1950).
12. REES, G. J. and GRAY, T C. *Brit J Anaesth.* 22. 83 (1950).
13. DAWKINS, C. J. M *Anaesthesia* 5 81 (1950).
14. KAPLAN, B. *Anaesthesia* 6 231 (1951).
- 15 MIDDLETON, H G and PICKEN, D K W *Brit Med. J.* 1192 (1954).
16. BARNETT, M S. *Anaesthesia* 9 153 (1954).