THE ANALGESIA OF METHOXYFLURANE*

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THE MANUFACTURERS of methoxyflurane (Penthrane®, Abbott) and several authors[1,2,3] make reference to the marked or profound analgesic qualities of this drug. Romagnoli[4] has observed its analgesic properties when used in the cyprane inhaler during the second stage of labour. He has also commented on the small amounts required to supplement nitrous oxide, also in the second stage of labour. Many of those who have used the drug have noticed that analgesia persists into the postoperative period.

I decided to use this drug in an attempt to produce the analgesic state during surgery, in the manner described by Artusio.[5] Previously, I have reproduced his work using nitrous oxide.[6] I found in the younger age group that nitrous oxide was too weak an agent. Both halothane and the azeotropic mixture of halothane and ether were found wanting.

The early studies of methoxyflurane were done by Artusio and Van Poznak.[7] It has proved to be a versatile agent which can be used alone or in a balanced technique. It has a high boiling point of 104.8° C., a low vapour pressure of 25 mm. Hg, and a high oil-water coefficient of 400. In the clinical range, it is non-explosive. Its odour is robust, fruity, but to the majority, pleasant. It is stable, and is not decomposed by air, light, or alkali.

This paper is a preliminary report on eleven cases using methoxyflurane alone to produce the analgesic state.

METHOD

Eleven candidates were studied during surgery. There were eight upper abdominal operations, one above-knee amputation, one bilateral varicose vein operation, and one mitral valvulotomy. Five were females and six males. The eldest was 87 years of age, and the youngest 34, the mean being 66 years. The physical status ranged from 1 to 3, with a mean of 2. In three cases, premedication consisted of meperidine 25–30 mg. with atropine sulphate 0.6 mg. The remainder received no premedication. The patients were anaesthetized with high flows of nitrous oxide and oxygen, and methoxyflurane vaporized outside the circuit in the B.O.C. Boyle's Ether Bottle. As soon as consciousness was lost, a transtracheal block was done using 2 c.c. of 4 per cent solution of lidocaine. This was immediately followed by paralysis with 60 mg. of succinylcholine. After endotracheal intubation, the patient was ventilated with a maximum concentration of methoxyflurane. This probably varied between 2.6 per cent[8] and 3.3 per cent[9]. With return of spontaneous respirations the nitrous oxide was discontinued, the

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oxygen flow set at 4 litres per minute, the plunger of the Boyle's bottle pulled right up, and the tap adjusted between the mid- and full-on position, depending on the concentration required to maintain analgesia.

Verbal contact was made with the patient. He was asked to open his eyes (Table I). He was told to nod his head up and down for "yes," and sideways for

TABLE I

CHARACTERISTICS OF ANALGESIC STAGE

	Stage 1		
	Plane 1	Plane 2	Plane 3
Amnesia	0	XXXX	XXXX
Response to spoken voice	XXXX	XXXX	XXXX –0
Cerebration	XXXX	XXXX	XXXXX–0
Memory for recent events	XXXX	XXXX	XX –0
Memory for past events	XXXX	XXXX	XXXX –0
Ability to focus eyes	XXXX	XXXX	XX –0
Ability to distinguish colour	XXXX	XXXX	XX –0
Taste	XXXX	XXXX	XXXX –0
Analgesia	0	XX	XXXX

"no." The concentration of methoxyflurane was adjusted to assure that the patient remained pain-free. This was affirmed by asking him whether he was comfortable. Muscle relaxation was obtained with a 0.2 per cent solution of succinylcholine using the "in and out" method. Respirations were assisted or controlled depending on the degree of muscle relaxation used.

In four patients, the percentage of vaporization was calculated while in the analgesic state.

All patients were followed in the postoperative period, and questioned with regard to amnesia.

RESULTS

Table II shows that the longest operating time was 5 hours, and the shortest was 1 hour. The maximum succinylcholine dose was 600 mg. and the least was

TABLE II

Operation	Age	Sex	Physical status	Operating time (hr. and min.)		Inducing dose thiopentone (mg)	Muscle relaxant (mg.)
Mitral valvulotomy	61	M	3	2	45	—	21 curare
Cholecysto-jejunostomy	70	M	3	3	—	—	260 s-choline
Gastro-enterostomy	72	F	3	3	—	—	20 curare
Abdominal hysterectomy	87	F	2	2	—	—	200 s-choline
A.K. left leg amputation	83	M	3	1	—	—	None
Bilateral vagotomy, gastro-enterostomy	76	F	2	4	30	—	450 s-choline
Bilateral varicose veins	66	F	2	2	30	—	None
Pyeleroplasty	65	M	3	2	15	—	300 s-choline
Gastrectomy	34	M	1	3	—	200	300 s-choline
Bilateral vagotomy, antrectomy	52	M	1	5	—	150	600 s-choline
Cholecystectomy, C. duct exploration	62	F	2	2	0	—	100 s-choline

60 mg. Two patients received *d*-tubocurare, while two received nothing further after their intubating doses.

In four patients, the amount of methoxyflurane used was noted and the percentage of vaporization calculated. The highest obtained was 0.43 per cent, and the lowest 0.34 per cent, with a mean of 0.39 per cent. With these concentrations, the muscle relaxation ascribed to this drug was not observed, and no success was obtained in this series by asking the patient to relax the abdominal muscles.

Operative behaviour was uneventful. There were no hypotensive episodes during induction or during the operation. Although no oscilloscope was used, the pulse was palpated almost continually and no arrhythmias were noted, other than those present preoperatively.

In the absence of relaxation, respirations were not depressed. In one case a Monaghan Ventilometer was used, which demonstrated a tidal volume of 250 ml. with a respiratory rate of 20 per minute. (This was in a 76-year-old female undergoing gastro-enterostomy.)

In one case, mild sweating occurred. This may have been associated with the fact that the patient was in plane 2 rather than plane 3 for a short period.

One unusual feature presented with this drug, in this state, which was not found with either ether or nitrous oxide, was that when verbal contact was attempted it took longer to reach the patient. The lid reflex was not a good indication of the analgesic state. The eyelids would have to be opened and the voice raised to arouse the patient from a "sleep-like" state. This arousal difficulty and drowsiness with the analgesia was seen to some degree or other in all the patients in the series.

All patients were seen several times postoperatively, and all did well. There were no respiratory or cardiac complications. There was total amnesia from the moment of loss of consciousness at the beginning of the operation until they were told the operation was over. Two patients died, one four weeks and the other six weeks after the operation, from pre-existing disease.

Discussion

The pertinent fact that emerges from this small preliminary series of cases is that methoxyflurane is a safe analgesic agent. A word of warning, however, must be given concerning the postoperative safety. Recently, Brody and Sweet[10] have reviewed in four cases the relationship between massive hepatic necrosis and administration of halothane. They suggest there is no proof, but the implication of a direct causal relationship is strong. They believed it was significant that three out of four of their cases had surgical procedures on the biliary tract. In this series one female patient, aged 62, underwent a cholecystectomy and common duct exploration, and another, aged 70, with carcinoma of the pancreas, a bilirubin of 7.6 mg. %, and very jaundiced, underwent a cholecysto-jejunostomy successfully.

No reports of hepatic damage associated with methoxyflurane have appeared in the literature. Cale, Parks, and Jenkins[11] studied gross overdosage in mongrel

dogs for five hours. The dogs were also exposed to a 15-minute period of hypoxia. Biopsy specimens of the liver and kidney removed at various postoperative periods were studied. A consistent change was watery vacuolization of the liver cells, thought to be a reversible and a non-specific process. The renal histological changes were not significant. I feel that the adequate oxygenation, absence of hypotension, and low percentage of methoxyflurane required (less than 0.42%) make hepatic necrosis extremely unlikely. Because of this report of hepatic necrosis associated with halothane administration, it is suggested that thought be given before methoxyflurane is used in the presence of hepatic disease during cholecystectomies or common duct explorations. However, we shall continue to use methoxyflurane in the presence of such conditions unless definite evidence of hepatic toxicity should appear.

General analgesia has proved to be a very useful technique over the years, particularly in the geriatric, poor-risk, or emergency case.[5,6,12,13,14]

The problem to date has been to find a satisfactory agent. Ether is an excellent agent and can only be discarded because sometimes, to maintain analgesia, the concentration must trespass into the explosive range.[15] Halothane and its azeotropic mixture were quickly abandoned, for they exhibited no analgesic properties at all. Dundee,[16] in his work, used subanaesthetic doses of various agents where he tested the tolerance of the subject to somatic pain. He estimated this by noting the amount of pressure applied by a metal disk to the anterior surface of the tibia before a sensation of pain was evoked. With the azeotropic mixture, some of his subjects noticed marked clouding of consciousness without any evidence of analgesia. Any doubt concerning this point can be dispelled by attempting to produce the analgesic state with halothane in oxygen! The patient passes rapidly from the unconscious to the wakeful state in no uncertain manner, however carefully the percentage of vaporization is controlled! Dundee suggests that the ability of a drug to produce analgesia in subanaesthetic concentrations and loss of consciousness in higher concentrations may be two separate entities mediated by different processes. I feel this theory may have much to commend it.

Dundee attempts to correlate these findings with those in previous studies of this particular series. Possibly the analgesic action of hypercarbia may be due to increases in the plasma-adrenaline concentration. Price[17] has shown that ether and cyclopropane, which possess marked analgesic properties, evoke considerable sympatho-adrenal activity. In contrast, halothane, which triggers off only minimal amounts of the catecholamines, has no analgesic action. Methoxyflurane does not fall into either of these categories. First, it is an excellent analgesic drug. Second, in concentrations of 0.5 per cent, it liberates even less catecholamines than halothane. It is doubtful that the lower percentage of 0.3–0.4 per cent would account for a serious increase in catechol liberation. Nevertheless, it is puzzling to find this difference between the two halogenated drugs.

In these 11 cases, and with many others in which conventional anaesthesia was used, no difficulty was found with induction. It has been reported that the slow induction is a drawback. This, I feel, is a safety factor. Although the drug has non-irritant properties, patients cough when presented with the maximum

concentration. This problem can be side-stepped, and induction hastened by positive pressure with maximum vaporization whilst under the paralysis of the intubating dose of succinylcholine.

The drowsiness associated with the analgesia was an unexpected finding. It is difficult to form too definite an opinion in such a small number of cases, but all patients appeared to be affected to some degree. I was reminded immediately of the very similar state which patients who have received conventional methoxyflurane anaesthesia present during emergence in the postanaesthetic room. Only one electroencephalogram was taken and reported to show low-voltage, fast-activity, and very similar to "light Pentothal" patterns. Tracings of the ascending reticular system would be of much greater interest. Magoun[18] has noticed fast activity from tracings of the ascending reticular system during the wakeful and analgesic state. It is interesting to speculate what these tracings might look like in view of the drowsiness, or depressed arousal state, found in the analgesia of methoxyflurane.

The highest percentage of vaporization was 0.43 per cent, the lowest 0.34 per cent, with a mean of 0.39 per cent. These calculations appear to be similar to those of Romagnoli[4].

Although prolonged recovery times have been a problem in conventional anaesthesia with methoxyflurane, this has not been a problem with analgesia. For methoxyflurane analgesia blood levels probably vary between 3 and 15 mg. %. With these low blood concentrations, high fat concentrations do not occur, as has been shown by Chenoweth and his workers.[19]

Occasional complaints have been made concerning the odour. The only way to overcome this is to use a closed circuit, or to exhaust exhaled gases from the operating room. Occasional headaches have been reported, but it is difficult to say whether they are due to the agent. Probably their incidence is much higher in poorly ventilated operating rooms. They have not been much of a problem in our department.

In conclusion, this preliminary report suggests that methoxyflurane is a safe and versatile agent to produce and to maintain the analgesic state for surgery.

Summary

A preliminary study was made of analgesia produced by methoxyflurane in oxygen in eleven patients undergoing surgery. Methoxyflurane was found to be safe and excellent as an analgesic agent. An associated drowsiness was also noticed, similar to that seen in the postanaesthetic period of conventional methoxyflurane anaesthesia. Methoxyflurane is compared with other agents and various theories discussed. It was felt that methoxyflurane, to date, was the agent of choice for this particular technique, especially in the geriatric, poor-risk, or emergency patient.

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