Summary

The incidence of recurrent calculi in the upper urinary tract is given.

The commonest causes of recurrence after operation are infection and imperfect removal of calculi at operation. Numerous other factors, some of which are not fully understood, play a part, and these are discussed.

I wish to thank Dr. J. Dawson for the calcium balance studies in Table IV, and Mr. J. Hainsworth for the photographic work. I also wish to thank my surgical colleagues in Leeds for allowing some of their cases to be followed up.

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LEVORPHAN IN ANAESTHESIA

BY

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The synthetic analgesic levorphan (methorphinan; "dromoran") has been used as a supplement to nitrous oxide and oxygen anaesthesia, and the results of an investigation, in which the drug was compared with pethidine for that particular purpose, have already been reported (Brown, 1952).

It seemed desirable to explore further the possibilities of levorphan in anaesthesia, and the present paper describes its use as premedication, and as a supplement to nitrous oxide and oxygen anaesthesia when given by continuous intravenous drip. Satisfactory clinical experience with levorphan as pre-operative medication has already been reported (Stoelting *et al.*, 1951).

Levorphan for Premedication

Before using the drug for premedication it was decided to determine the time of onset of action after subcutaneous injection, the time before maximum analgesia was observed, and the total duration of action. This was studied in several patients with post-operative pain and in one patient with severe nerve-root pain due to vertebral collapse. The results were as follow: (*a*) the time interval between the injection and the onset of analgesia averaged 20 minutes (range 15–25 minutes); (*b*) the maximum analgesic effect occurred within one and a half hours of injection; (*c*) the duration of analgesia, after injection of one ampoule (2 mg.), was seven hours (in very severe pain).

After the period of maximum analgesia the effect of the drug gradually wore off. There appeared to be a marked cumulative action, since, once analgesia had been established by giving 4 mg. in divided doses, satisfactory freedom from pain could be maintained by use of 0.5 mg. every twelve hours. After the above points were established, levorphan was used as premedication in a series of 100 patients about to undergo a general surgical or gynaecological operation. Levorphan alone was given to 30 patients (series A), levorphan and atropine to 20 patients (series B), and levorphan and scopolamine to 50 patients (series C). All the drugs were given by subcutaneous injection. A record card was designed to give the following data: age, sex, build, and type of patient, the presence or absence of pain, the time premedication was given, and the time of induction of anaesthesia. The patient's "normal" pulse rate, the pulse rate immediately before induction, the presence or absence of drowsiness, respiratory depression, and amnesia were also noted.

Dosage.—Two mg. of levorphan was the standard premedication. In 30 patients it was the only drug used for premedication, atropine, 1/100 gr. (0.65 mg.), being given when anaesthesia was induced with thiopentone (series A). Levorphan, 2 mg., and atropine, 1/100 gr. (0.65 mg.), were given to all 20 patients in series B except three as follows: (1) a 57-year-old patient with prolapse, levorphan, 1.5 mg., and atropine, 1/100 gr. (0.65 mg.); (2) a 55-year-old patient with prolapse, levorphan, 1 mg., and atropine, 1/100 gr. (0.65 mg.); and (3) a 63-year-old patient with diverticulitis, levorphan, 1 mg., and atropine, 1/100 gr. (0.65 mg.). Levorphan, 2 mg., and scopolamine, 1/150 gr. (0.43 mg.), were given to 50 patients in series C. No attempt was made to give the drug at a constant time before induction, and in fact the interval varied from half an hour to five hours. The time lapse between premedication and induction is shown in Table XII.

Results

Before anaesthesia was induced and before the pulse rate was recorded an assessment of the result of the premedication was made. The figures resulting from this observation are given as Table I. It is concluded that there is no difference among the three series of patients with regard to post-premedication state. As "omnopon" and scopolamine form the combination of drugs most often used as premedication it was decided to compare the assessment of the patients comprising series C with a control series who had been given omnopon, ¼ gr. (22 mg.), and scopolamine, 1/150 gr. (0.43 mg.). Figures for this control group are given as Table II. The 50 members of the control group were chosen by taking record cards at equal intervals from a file containing the cards of 500 patients.

TABLE I.—*Clinical Assessment of Post-premedication State*

	Series A	Series B	Series C
Apprehensive	11 (37%)	3 (15%)	12 (24%)
Satisfactory	19 (63%)	17 (85%)	37 (74%)
Oversedated	—	—	1 (2%)
Total	30 (100%)	20 (100%)	50 (100%)

TABLE II.—*Clinical Assessment of Post-premedication State of Control Group*

	Control Group
Apprehensive	7 (14%)
Satisfactory	43 (86%)
Oversedated	—
Total ..	50 (100%)

On combining the oversedated with the satisfactory, the results given in Table III are obtained. These show no evidence of difference between the two series of patients.

In addition to the above clinical assessment, specific note was taken of (*a*) the presence or absence of drowsiness as

reported by each patient in response to a question, (*b*) the presence or absence of respiratory depression, (*c*) the occurrence or not of nausea, and (*d*) the presence or absence of amnesia as shown by each patient's recollection (or not) of the journey to the operating theatre and of thiopentone injection. The figures for these observations are recorded as Tables IV, V, VI, VII, and VIII. The three series of patients differ with regard to the incidence of reported drowsiness. The main difference is clearly between series A on the one hand, with 23% of patients drowsy, and series B and C on the other hand, with 55% and 58% respectively of patients drowsy.

Table IV shows that the incidence of drowsiness is less among series A than among series B and C together. Scrutiny of Table IX for the first four hours of premedication gives no indication either for series A or for series B that the incidence of drowsiness is significantly different for the period 2–4 hours from what it is for the period 0–2 hours; similarly, there is no evidence of difference for series C.

Table X records alteration of pulse rate in each of the three series of patients. The degree of sedation can be judged in part by this alteration, the rate immediately before induction of anaesthesia being compared with the patient's normal rate. This table shows that the three series of patients differed with regard to alteration of pulse rate. It is clear that the main difference is between series C and the other two series together, and that this difference is that in series C a smaller proportion of patients tend to have an increase in pulse rate and a larger proportion to have a decrease. The duration of the sedative effect was gauged from the relation between alteration of pulse rate and the interval between premedication and induction of anaesthesia. This relation is shown in Table XI. In none of the three series of patients do the figures suggest any significant increase in the incidence of patients with increased pulse rate (nor with decreased pulse rate) between the first and second two-hour period.

The figures in Table XII suggest no statistically significant difference between the three series of patients with regard to time of premedication.

TABLE III.—*Comparison of Clinical Assessments of Post-premedication State of Control Group with that of Series C*

	Series C	Control Group
Apprehensive	12 (24%)	7 (14%)
Satisfactory or oversedated	38 (76%)	43 (86%)
Total	50 (100%)	50 (100%)

TABLE IV.—*Drowsiness*

	Series A	Series B	Series C
Drowsy	7 (23%)	11 (55%)	29 (58%)
Not drowsy	23 (77%)	9 (45%)	21 (42%)
Total ..	30 (100%)	20 (100%)	50 (100%)

TABLE V.—*Respiratory Depression*

	Series A	Series B	Series C
Respiratory depression ..	2 (6·7%)	—	3 (6·0%)
No respiratory depression	28 (93·3%)	20 (100%)	47 (94·0%)
Total ..	30 (100%)	20 (100%)	50 (100%)

TABLE VI.—*Nausea*

	Series A	Series B	Series C
Nausea	2 (6·7%)	3 (15·0%)	—
No nausea	28 (93·3%)	17 (85·0%)	50 (100%)
Total ..	30 (100%)	20 (100%)	50 (100%)

TABLE VII.—*Recollection of Journey to the Theatre*

	Series A	Series B	Series C
Journey not remembered	—	2 (10%)	6 (12%)
Journey remembered ..	30 (100%)	18 (90%)	44 (88%)
Total ..	30 (100%)	20 (100%)	50 (100%)

TABLE VIII.—*Recollection of Thiopentone Injection*

	Series A	Series B	Series C
Injection not remembered	4 (13·3%)	3 (15%)	17 (34%)
Injection remembered ..	26 (86·7%)	17 (85%)	33 (66%)
Total ..	30 (100%)	20 (100%)	50 (100%)

TABLE X.—*Alteration in Pulse Rate (Pre-induction Pulse Rate compared with "Normal")*

Alteration in Pulse Rate (Beats/Minute)	Series A	Series B	Series C
+11 or more	14 (47%)	10 (50%)	9 (18%)
−10 to +10	16 (53%)	8 (40%)	28 (56%)
−11 or more	—	2 (10%)	13 (26%)
Total ..	30 (100%)	20 (100%)	50 (100%)

Conclusions from Premedication Series

I.—(*a*) Clinical assessment has shown (Table I) that satisfactory sedation was achieved in 73% of the 100 cases studied, and in 63% of the 30 cases given levorphan alone. (*b*) It is shown in Table X that 67% of the 100 cases studied showed either a decrease in pulse rate or an increase not greater than 10 beats a minute. Among the 30 patients given levorphan alone, 53% had an alteration in pulse rate not greater than ±10 beats a minute. The remaining 47% had an increase of 11 or more beats a minute, and this compares with 27% of the 70 patients in the other two series. Statistical analysis shows (Table X) that in series C (for which scopolamine was added to levorphan) the tendency against acceleration or towards retardation of pulse rate was significantly greater than in series B (for which atropine was added) and series A (for which levorphan was given alone). (*c*) Comparison of series C with a control group of 50 patients taken at random from 500 who had received premedication with omnopon, ½ gr. (22 mg.), and scopolamine, 1/150 gr. (0.43 mg.) (Table II) shows no significant evidence of difference with regard to clinical assessment of sedation. (*d*) From I (*a*), (*b*), and (*c*) above, it is concluded that levorphan has a definite sedative effect.

II.—As judged by the alteration in pulse rate (Table XI) no indication is given that the sedative effect of levorphan (either by itself or in combination with atropine or scopolamine) tends to wear off within the first four hours after subcutaneous injection.

TABLE IX.—*Incidence of Drowsiness Related to Time of Premedication*

	Time (h) of Premedication (Hours before Operation)								
	Series A			Series B			Series C		
	0 < h ≤ 2	2 < h ≤ 4	4 < h	0 < h ≤ 2	2 < h ≤ 4	4 < h	0 < h ≤ 2	2 < h ≤ 4	4 < h
Not drowsy	8 (72·7%)	13 (76·5%)	2 (100%)	3 (33·3%)	5 (50%)	1 (100%)	5 (25%)	14 (50%)	2 (100%)
Drowsy	3 (27·3%)	4 (23·5%)	—	6 (66·7%)	5 (50%)	—	15 (75%)	14 (50%)	—
Total ..	11 (100%)	17 (100%)	2 (100%)	9 (100%)	10 (100%)	1 (100%)	20 (100%)	28 (100%)	2 (100%)

TABLE XI.—*Relation Between Pulse Rate Alteration and the Interval Between Premedication and Induction*

Alteration in Pulse Rate (Beats/Minute)	Time (h) of Premedication (Hours before Operation)								
	Series A			Series B			Series C		
	0<h≤2	2<h≤4	4<h	0<h≤2	2<h≤4	4<h	0<h≤2	2<h≤4	4<h
+11 or more..	6 (54·5%)	7 (41·2%)	1 (50%)	6 (66·7%)	3 (30%)	1 (100%)	3 (15%)	5 (17·8%)	1 (50%)
−10 to +10	5 (45·5%)	10 (58·8%)	1 (50%)	2 (22·2%)	6 (60%)	—	11 (55%)	17 (60·8%)	—
−11 or more..	—	—	—	1 (11·1%)	1 (10%)	—	6 (30%)	6 (21·4%)	1 (50%)
Total ..	11 (100%)	17 (100%)	2 (100%)	9 (100%)	10 (100%)	1 (100%)	20 (100%)	28 (100%)	2 (100%)

TABLE XII.—*Time of Premedication*

Time (h) of Premedication (Hours before Operation)	Series A	Series B	Series C
0<h≤2	11 (36·7%)	9 (45%)	20 (40%)
2<h≤4	17 (56·6%)	10 (50%)	28 (56%)
4<h	2 (6·7%)	1 (5%)	2 (4%)
Total ..	30 (100%)	20 (100%)	50 (100%)

III.—(*a*) Of the patients given levorphan alone, 23% said that they felt drowsy (Table IV). In series B and C (for which atropine and scopolamine respectively were added to the levorphan) the figure rose to 57% of the 70 patients, the difference being statistically significant. (*b*) From III (*a*) above it is concluded that levorphan has a slightly hypnotic effect. (*c*) The investigation (Table IX) gives no indication that the hypnotic effect of levorphan, either alone or in combination with either of the other two drugs, tends to wear off within the first four hours after subcutaneous injection.

IV.—(*a*) Of the 100 cases studied, 5% showed respiratory depression (Table V). The investigation gives no indication of difference in this respect among the three series of patients given levorphan only, levorphan plus atropine, and levorphan plus scopolamine. In all five cases the respiratory depression was mild. (*b*) From IV (*a*) above it is concluded that levorphan tends to depress respiration slightly.

V.—Nausea was observed in 5% of the 100 cases studied, and was severe in one case. Two of the cases were in series A, three in series B, and none in series C; but the differences are not significant.

VI.—(*a*) All 30 patients given levorphan alone stated that they remembered the journey to the theatre (Table VII), and 26 of them (86.7%) stated that they remembered the injection of thiopentone (Table VIII). Among the whole 100 patients studied, 92% said they remembered the journey and 76% said they remembered the injection. (*b*) The three series do not differ in either of these two respects; but, bearing in mind that the injection may not even be noticed by the patient, it is concluded that levorphan has shown no evidence of an amnesic effect in this investigation.

VII.—From I to VI above it is concluded that levorphan given with atropine or scopolamine is satisfactory for premedication; but, except for the long duration of action, has no advantages over omnopon or morphine.

Nitrous Oxide and Oxygen Supplementation by Intravenous Drip

Following the previous investigation of levorphan as a supplement to nitrous oxide and oxygen anaesthesia by the intermittent injection technique, it was decided to investigate the use of the drug for the purpose when given as a continuous intravenous drip infusion. It was found that, in order to build up sufficient analgesia, the drip had to be given at a rate liable to result in respiratory depression. The incidence of respiratory complications following operations performed under this anaesthesia was increased significantly.

Summary

Levorphan has been used as premedication in a series of 100 patients and as a supplement by continuous drip to nitrous oxide and oxygen anaesthesia in 25 patients. For premedication the drug was found satisfactory, although it did not cause amnesia. It is suggested that as a continuous drip levorphan is contraindicated because of the high incidence of respiratory depression.

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Medical Memoranda

Perforation of Both Tympanic Membranes During Anaesthesia

This case is reported because it would appear to be most unusual. I could not find any record of a similar occurrence in the literature.

CASE REPORT

A healthy man aged 30 was operated upon for chronic appendicitis on August 22, 1953. Laparotomy was performed under general anaesthesia. Induction was begun with thiopentone sodium, 0.4 g., followed by succinylcholine chloride, 50 mg. A size 9 rubber Magill endotracheal tube was passed orally under direct vision without any difficulty. A Waters metal airway, size 3, was inserted alongside the endotracheal tube. A rubber face-piece was applied over a piece of gamgee and anaesthesia maintained with gas, oxygen, and trichlorethylene, using a Boyle machine on a semi-open circuit. A few minutes later gallamine triethiodide, 80 mg., was administered, followed by a further 40 mg. about 10 minutes later. Assisted respiration was required for about 10 minutes, and was performed by compressing the rubber rebreathing bag and partly closing the expiratory valve. No undue force was used in this manœuvre, and free air entry into the respiratory passage was seen and heard.

The operation, which lasted about 40 minutes, progressed without any complications. When it was completed the patient was bleeding from both ears, and the opinion of an E.N.T. surgeon was sought.

The patient was examined 10 minutes after the operation had been completed. He was then waking up from the anaesthesia. On examination, bleeding was seen from both ears. Haematotympanum was found on examination of the left ear, and the tympanic membrane was seen to be very thin and atrophic, and to be perforated in the attic region. On examination of the right ear blood was escaping from the external auditory meatus, haematotympanum was present, the tympanic membrane was very thin and atrophic, and a large triangular posterior perforation was present. On close examination of this triangular perforation a flap of the membrane was found; the pressure of the escaping fluid