L-METHORPHINAN AS A SUPPLEMENT TO NITROUS OXIDE AND OXYGEN ANAESTHESIA

BY

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The use of pethidine as an adjunct to nitrous oxide and oxygen anaesthesia was first reported by Neff *et al.* (1947) in the U.S.A. and by Mushin and Rendell-Baker (1949) in Great Britain. The value of this anaesthetic technique has since been confirmed by several other workers, including Brotman and Cullen (1949). Brotman *et al.* (1950) have investigated the properties of other analgesics used by the same technique and have compared pethidine with morphine and a new synthetic substance, methorphanin. In the United States the racemic form of methorphanin is commercially available. The compound manufactured in this country and in Europe is the laevo-tartrate of methorphanin. Its pharmacology has been described by Randall and Lehmann (1950) and by Fromherz (1951). The drug is said to be more potent, weight for weight, than morphine, comparable analgesic doses having a longer action and causing less respiratory depression. The laevo-tartrate is about twice as potent as the racemic compound weight for weight.

When supplies of L-methorphanin ("dromoran") became available in this country it was decided to investigate its effects as an adjunct to nitrous oxide and oxygen anaesthesia in a series of 100 patients, all of whom were undergoing major surgery. The only contraindication to the use of the drug was the absence of suitable veins in the upper limb. The results were recorded on Nosworthy cards type 1. Premedication consisted of "omnupon," $\frac{1}{4}$ gr. (22 mg.), and scopolamine, 1/150 gr. (0.43 mg.), one and a half hours before operation. In patients over 60 years of age morphine, $\frac{1}{4}$ gr. (11 mg.), and atropine, 1/100 gr. (0.65 mg.), were given one hour before.

Technique and Normal Findings

Anaesthesia was induced with thiopentone, 0.5 g., in all cases, the rate of injection being markedly reduced in poor-risk or older patients. Anaesthesia was maintained with nitrous oxide (5 litres a minute) and oxygen (2 litres a minute) with a Boyle anaesthetic machine in a semi-closed circuit. If muscle relaxation were required or an endotracheal tube were necessary, D-tubocurarine chloride or gallamine triethiodide was injected. (Note: L-methorphanin precipitates with thiopentone, but is miscible with D-tubocurarine chloride and gallamine triethiodide.)

A Gordh needle was inserted into a suitable arm vein, and an injection of L-methorphanin was given as soon as the effect of the thiopentone (with or without relaxant) on respiration was wearing off. This was usually about five minutes after the injection of thiopentone. Further injections of L-methorphanin and the relaxant were given through the Gordh needle as required. At the end of operation, if a relaxant had been given and its effects were still present, atropine, 1/100 gr. (0.65 mg.), intravenously, followed directly by neostigmine, 2.5 mg., was given. Before the patient left the theatre the pharyngeal reflex was tested and its presence or absence noted.

An exception to the above technique was made during the repair of hiatal hernia by the transthoracic approach.

Anaesthesia was maintained with nitrous oxide (1 litre a minute) and oxygen (500 ml. a minute) with a Waters absorber with an intentional leak.

After intravenous injection in the anaesthetized patient the effect of L-methorphanin can be observed in three to five minutes. In this series the average case was given 0.5 mg., which was repeated if and when necessary. Less fit patients received an initial dose of 0.25 mg., repeated as required.

The average duration of effect of the first 0.5 mg. of L-methorphanin was 18 minutes (range 0-60, standard deviation 26.5). The average duration of effect of the first 1 mg. of L-methorphanin was 43 minutes (range 10-150, standard deviation 27.02). It was rarely necessary to exceed 1.5 mg. of L-methorphanin, and no case received more than 2 mg.; 69% of the patients received 1 mg. or less. No depression of respiration occurred in normal cases with the above dosage of L-methorphanin. In very poor-risk patients there was a slight depression, a reduction in respiratory rate rather than depth, but less marked than with pethidine. Bronchospasm was not seen. The impression was gained that the bronchial tree was dilated.

Of the cases treated with L-methorphanin 93% had an active pharyngeal reflex before leaving the theatre, and almost all were awake on return to the ward. The majority, once back in bed, fell asleep. Those that remained awake had good analgesia with no restlessness.

Criteria

If during anaesthesia any respiratory or circulatory upset occurred, the case was not classified as "administration satisfactory."

"C.V.S. disturbance" includes surgical shock, haemorrhage, and fluctuations in pulse and blood pressure due to surgical manipulations, in addition to the effects of the anaesthetic on circulation.

"Respiratory disturbance" includes depression due to thiopentone and the relaxant, and tachypnoea, in addition to the effect of the drug under investigation. It also includes the effects of position.

During the post-operative period, if the patient had a cough with no other symptoms or signs he was assumed to have developed a minor respiratory post-operative complication. This strict classification resulted in a higher incidence than that usually reported.

If the patient was found to have a minor respiratory complaint in the pre-operative examination it was often difficult to determine, in the post-operative period, whether or not this complication had increased. In cases of doubt it was assumed to have done so, and the patient was classified as having a minor respiratory post-operative complication.

Results

In Great Britain at present pethidine seems to be the drug of choice for supplementation of nitrous oxide and oxygen anaesthesia, and most anaesthetists are familiar with its action. The following results of a trial with L-methorphanin are therefore compared, where possible, with those obtained in an earlier series of 100 cases in which pethidine was used. In this series the average patient was given 25 mg. of pethidine, the dose being repeated as required. The sex and age distribution of the patients in each series are given in Tables I and II.

TABLE I.—Sex Distribution of Cases

	L-Methorphanin Series	Pethidine Series
No. of males	42	42
No. of females	58	58
Total	100	100

TABLE II.—Age Distribution of Cases

	L-Methorphanin Series	Pethidine Series
0-10 years	0	0
11-20 " " " " " " ..	6	4
21-40 " " " " " " ..	26	26
41-60 " " " " " " ..	46	45
61 years+ " " " " " " ..	22	25
Total	100	100

Table III shows the pre-operative state of patients in both series. They were classified as "good" only if there were none of the pre-operative complications shown in Table IV. This table refers only to 66% of the L-methorphanin series and to 70% of the pethidine series. It should be emphasized that more than one pre-operative complication might have occurred in any one patient.

TABLE III.—Pre-operative Physical State

	L-Methorphanin Series	Pethidine Series
Good	34	30
Fair " " " " " " ..	48	53
Poor " " " " " " ..	16	16
Serious " " " " " " ..	2	1
Total	100	100

TABLE IV.—Incidence of Pre-operative Complications

Complication	L-Methorphanin Series	Pethidine Series
Incomplete data	3	5
Respiratory, major	1	2
Respiratory, minor	29	22
C.V.S.	30	34
C.N.S.	6	5
G.U.	4	3
Gastro-intestinal	3	8
Metabolic	6	13
Total	82	92

TABLE V.—Incidence of Complications During Anaesthesia

	L-Methorphanin Series	Pethidine Series
Emergency	0	1
I.V. therapy	20	22
C.V.S. disturbance	11	11
Respiratory disturbances	10	8
Administration satisfactory	78	80
Total	119	122

TABLE VI.—Post-operative Complications

	L-Methorphanin Series	Pethidine Series
Technical	0	1
Respiratory, major	2	3
Respiratory, minor	39	21
C.V.S. first 24 hours	6	4
C.V.S. later	1	2
C.N.S.	1	2
G.U.	14	11
Other	6	4
None of above	41	62
Total	110	110

The complications arising during anaesthesia are given in Table V. The outstanding difference between the L-methorphanin and the pethidine series is the incidence of minor respiratory post-operative complications, and this is reflected in the "none of above" category (Table VI). For reasons already given this figure cannot be absolutely accurate, and there was a slightly higher incidence of pre-operative minor respiratory upsets in the L-methorphanin series.

In the L-methorphanin series there were six cases classified as "other." They were: obstructive jaundice which developed cholaemia; paralytic ileus; diarrhoea; numbness in arm (not used for intravenous injection or placed on arm-board) with no objective signs—disappeared without treatment; exacerbation of rheumatoid arthritis; and jaundice, from blood transfusion. In the pethidine series the four "other" cases consisted of a case of carcinoma of the uterus in which ascites developed; a case of jaundice following blood transfusion; and two cases of diarrhoea with blood and mucus in the stools. In the pethidine series the post-operative complication classified as "technical" consisted of minor trauma to the gums from laryngoscopy.

There was one death in the L-methorphanin series: the patient who had had a cholecystojejunostomy performed for obstructive jaundice developed cholaemia and died on the tenth day after the operation. There were two deaths in the pethidine series—one from pulmonary embolus on the tenth day, and one a few hours after operation from the inhalation of intestinal contents following the rupture of the cuff of an endotracheal tube.

The majority of patients classified as vomiting (Table VII) for "0-12 hours" vomited once or twice. In many cases this resulted from the early awakening and too early drinking, the first mouthfuls swallowed being immediately returned. Routine post-operative sulphonamide therapy was given in gynaecological cases. When post-operative vomiting occurred in such patients it was impossible to say whether the cause was the sulphonamide or the anaesthetic.

Table VIII shows the numbers in which the pharyngeal reflex was recovered in the theatre.

TABLE VII.—Post-operative Vomiting

	L-Methorphanin Series	Pethidine Series
None	60	64
0-12 hours	29	28
12-24 " " " " " " ..	5	3
Over 24 " " " " " " ..	6	5
Total	100	100

TABLE VIII.—Return of the Pharyngeal Reflex in the Theatre

	L-Methorphanin Series	Pethidine Series
Reflex recovered	93	85
Reflex not recovered	7	15
Total	100	100

The L-methorphanin and pethidine series were comparable as regards site and severity of operation, each series consisting of patients selected at random requiring anaesthesia for major gynaecological, orthopaedic, or general surgical operations. Since L-methorphanin is said to have a persistent analgesic action, it was thought that the duration of post-operative analgesia might be of interest.

Only 29% of cases required an analgesic during the first four hours after the last injection of L-methorphanin during the operation, 28% did not require any during the first 12 hours, and 17% required no analgesic. It was found that the duration of post-anaesthetic analgesia was not dependent on the dose of L-methorphanin given during the operation.

Conclusions

L-Methorphanin is a powerful analgesic drug with a long action.

Its intravenous administration does not result in any untoward reactions.

By the intravenous route it is a satisfactory adjuvant to nitrous oxide and oxygen anaesthesia, when it behaves in a similar fashion to pethidine.

The drug is worthy of a more complete investigation in anaesthesia.

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NEURINOMA OF THE STOMACH REMOVED BY TOTAL GASTRECTOMY

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Neurogenic tumours of the stomach are infrequent, as is shown by the small number of cases reported in the available literature. Thus, Podlaha, Simon, and Uher (1934) mention only 2 out of 741 cases of benign tumours of the stomach. Minnes and Geschickter (1936) found that 10.9% of 931 benign tumours were of neurogenic origin. Judd and Hoerner (1936) observed one neurinoma in 50 cases. As regards the frequency of benign tumour of the stomach, Finesilver (1942) found 6 in a total of 43,200 x-ray examinations of the stomach carried out at a New York hospital. In Greece, Professor Courias (1946) reported one case of gastric schwannoma. Another case was operated upon by Dr. M. Maccas a year later. In the literature neurogenic tumours appear under different names, such as neurinoma, perineural fibroblastoma, schwannoma, neurilemmoma. It is not our intention to expound on the origin or the pathological classification of the neurogenic tumours.

The site of these tumours coincides with that of the malignant ones. Judd and Hoerner report that 66% developed in the antrum, 24% in the corpus, and 10% in the cardiac region. Their size varies from a chick-pea to a man's fist or more. Thus Sanguily and Blanco (1945) report a case of gastric schwannoma in which the tumour was 17 by 9 by 5 cm. in size and 580 g. in weight. Tierny (1934) reports a case in which a schwannoma was 250 g. in weight.

Symptoms depend on the size and position of the tumours. Small ones may remain latent, provided they are not ulcerated and not situated near the pylorus, in which case they are followed by symptoms of stenosis. The tension and torsion of pedunculated tumours situated in the pyloric region may possibly produce dilatation of the stomach accompanied by vomiting and visible peristalsis. These symptoms, however, may disappear when the tumour untwists. Larger tumours cause gastric disturbances—for example, pain after eating, vomiting, etc. These symptoms are usually more pronounced in the case of ulcerated tumours.

Mallory (1920) believes that ulceration is due to obstruction of the vessels, followed by necrosis of the mucosa. According to Judd and Hoerner, ulcerated tumours amount to 32%. West and Knox (1948) report that five out of six cases of gastric neurinoma were ulcerated. Another characteristic of these tumours is repeated bleeding. West and Knox report that four of their six cases had severe bleeding, and that in one case haemorrhage, though moderate, was continuous.

Anaemia is a characteristic symptom of neurogenic tumours; therefore Finesilver recommends an x-ray examination of the stomach of anaemic patients. According to Sanguily and Blanco, large tumours cause a weakening of the muscular tone of the stomach, resulting in slow evacuation of the contents, while small tumours stimulate peristalsis and raise the tone.

Diagnosis and Treatment

Diagnosis is based on clinical examination and laboratory research. In the case of small tumours, apart from occasional slight muscular tension at the epigastrium, no other symptoms are found. Tumours producing stenosis of the pylorus are followed by the corresponding symptoms. Radiological examination of neurogenic tumours may show a filling defect. The regular contours of the displaced mucosa are usually preserved. In many cases a niche due to central ulceration of the tumour is seen. The folds of the mucosa are normal. Peristalsis persists at the region of the filling defect, while spasm is lacking. These characteristics are useful in the differential diagnosis from malignant tumours and ulcers. Spasm exists only in the case of tumours situated near the pylorus. Routine laboratory examination of the gastric juice, stool, etc., may disclose the presence of blood. Blood examination often demonstrates secondary anaemia.

Finesilver points out that in the case of anaemic patients achlorhydria, and a filling defect with regular contours of the stomach at x-ray examination, probably signify the presence of a benign tumour.

The treatment for neurinoma is, of course, surgical, in order to prevent the danger of haemorrhage and of malignant change. The latter possibility is estimated by Paul and Chapman (1945) at 10%. Malignancy is usually represented by neurogenic sarcomas. In a case of suspected malignancy, partial or total gastrectomy is recommended. Tumours causing pyloric stenosis are also treated by gastrectomy. In the six cases of West and Knox, three partial gastrectomies and three local excisions were done. Should a benign neurogenic tumour be diagnosed before operation, local extirpation is recommended by most authors (Lockwood, 1932; Finesilver, 1942; Paul and Chapman, 1945; Sanguily and Blanco, 1945; West and Knox, 1948; Weeder and Stayman, 1950). Weeder and Stayman, however, point out the frequency of recurrence. The difficulty in determining the benign nature of the tumour, the tendency to recurrence, and the possibility of malignant change are in favour of partial gastrectomy.

The size and situation of the tumour are an important factor in determining the type and extent of gastrectomy. In our case the large area covered by the tumour, and its extension to the cardia of the stomach, forced us to perform a total gastrectomy. The progress of anaesthesia and re-animation has greatly lessened the risks of total gastrectomy and post-operative complications are usually successfully treated. It is recommended, however, that such patients be closely followed up.

Case Report

On March 7, 1952, a 40-year-old woman, complaining of weakness and vague abdominal discomfort, was admitted to the second surgical clinic of Athens University. The history dated back seven years. During this period she had suffered