transient epithelitis, which subsided within the next weeks. No evidence of more severe tissue reaction was observed. None of the patients treated experienced radiation sickness characterized by the symptoms of lassitude, anorexia, nausea, or vomiting.

We know that the number of patients studied is not large enough or the time of observation long enough for conclusive evaluation of this method of treatment. However, we feel that the results to date are encouraging. Complete regression of the tumour was accomplished in cases of really superficial lesions. It is realized that any anatomical classification based on cystoscopic findings is subject to error. None the less, we believe that when the clinical findings are favourable this therapy should be considered as a primary measure.

Summary

Intracavitary instillation of colloidal radioactive gold (^{198}Au) was used for treatment of patients with multiple papillomata of the bladder. Approximately 300 mc. of gold was instilled into the bladder for four to six hours to deliver a dose of about 4,000 to 5,000 r to the bladder epithelium. The treatment had no harmful side-effects locally or on the general condition of the patient.

Three selected cases suitable for radioactive gold therapy are briefly reported.

It is our impression that this method is an excellent type of irradiation for really superficial malignant lesions. The method was used for treatment of multiple papillomatosis of the bladder alone or in conjunction with surgery.

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DIPIPANONE HYDROCHLORIDE AS AN ADJUNCT TO ANAESTHESIA IN OBSTETRICS AND SURGERY

BY

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Balanced anaesthesia developed over recent years has been made possible by the introduction of a large range of drugs with specific actions. In 1947 Neff, of San Francisco, introduced pethidine into anaesthetic practice as an adjunct to nitrous oxide anaesthesia. Since then pethidine has proved itself as useful in the operating theatre as in the general and obstetric wards. Over the past 18 months we have investigated the use of another analgesic, dipipanone hydrochloride, in obstetrics and as an adjunct to general anaesthesia. This paper describes our results.

Pharmacology

Dipipanone hydrochloride (DL-6-piperidino-4,4-diphenylheptan-3-one), which is the piperidino analogue of meth-

adone ("physeptone"), was first described by Ofner, Thorp, and Walton in 1949. Its analgesic properties in animals were investigated by Ofner, Walton, Green, and White (1950) and by Green and Young (1951). Its use as an analgesic for the control of post-operative pain and that arising from a variety of acute and chronic medical conditions has been

Dipipanone hydrochloride

Methadone

reported on by Gillhespy, Cope, and Jones (1956). In man 25 mg. of dipipanone administered intramuscularly or subcutaneously is equi-analgesic with 10 mg. of morphine, 100 mg. of pethidine, or 10 mg. of methadone. The analgesic effect develops within 15 minutes and lasts from five to six hours. Nausea and vomiting are rare and there is no significant change in the blood pressure or pulse rate. As with morphine, the respiratory minute-volume is reduced mainly by a reduction in the respiratory rate; this effect, however, is less than that of an equi-analgesic dose of morphine. There is no appreciable hypnotic effect, and prolonged administration produces no significant change in the blood picture.

Dipipanone hydrochloride, like methadone, is metabolized in the liver and excreted in the faeces and urine. Therefore it should be used with caution in patients with severe liver or kidney disease.

Methods

Clinical Material.—The cases investigated were (1) a series of 53 consecutive obstetric cases which received dipipanone to relieve pain in labour (as a control pethidine was used in a further series of 53 consecutive cases); (2) a series of 200 general surgical cases which received dipipanone as an adjunct to general anaesthesia, and (3) a series of 100 thoracic surgical cases in which dipipanone was the main supplement to nitrous oxide anaesthesia and was used in place of a muscle relaxant.

Obstetric Cases.—During a period of one month, 53 consecutive patients were given dipipanone hydrochloride for the relief of pain in labour. As a control, a similar number of cases were treated with pethidine. For ease of statistical analysis, the midwife present at each delivery recorded the particulars of the case, the dose of analgesic given, the relief obtained, and the progress of labour on a specially designed form. The similarity of the two series of cases with respect to age and body weight will be seen from Table I.

General Surgical Cases.—Anaesthesia for the general surgical cases followed a standard technique. The patients were premedicated with papaveretum ("omnupon"), $\frac{1}{2}$ gr. (20 mg.), and hyoscine, 1/150 gr. (0.43 mg.), or with

TABLE I.—Age and Weight of Obstetric Patients

Age in Years:	15–	20–	25–	30–	35–	40–45	Total
Dipipanone	3	20	17	11		2	53
Pethidine	5	26	15	4	1	2	53

Weight in Stones:	8–	9–	10–	11–	12–	13–	14–	Total
Dipipanone	7	12	14	9	7	1	3	53
Pethidine	10	9	19	10	3	2		53

morphine, $\frac{1}{4}$ gr. (10 mg.), and atropine, 1/100 gr. (0.65 mg.), subcutaneously. After induction with thiopentone, anaesthesia was maintained with nitrous oxide and oxygen. The initial dose of dipipanone was given intravenously, the dose being graded according to the patient's age, weight, and physical condition, and varied from 2.5 to 5 mg. The concentration of dipipanone found most convenient was 2.5 mg. per ml. When an endotracheal tube was passed, 50 mg. of suxamethonium was given and gallamine triethiodide was injected later in divided doses if full muscular relaxation was required. The adequacy of the initial dose of dipipanone was judged from the respiratory rate. A rate of 10 to 12 respirations a minute was aimed at, and when this returned to 16 to 18 a minute a further dose of dipipanone was given. It must be stressed here that patients may easily receive an overdose if subsequent doses are given at fixed intervals without reference to the respiratory rate. The nature of the operations performed is shown in Table II.

TABLE II.—Operations Performed in 200 General Surgical Cases

Hernia	27	Thyroidectomy (toxic) ..	4
Cystoscopy	18	D + C	4
Partial gastrectomy ..	16	Fothergill repair	4
Vaginal hysterectomy and repair ..	13	Cholecystectomy	3
Tonsils and adenoids ..	13	Cystoscopy, vasotomy, and suprapubic prostatectomy ..	3
Abdominal hysterectomy and appendicectomy ..	12	Varicose veins	2
E.U.A.	12	Orchidectomy	2
Dental roots extraction ..	11	Thyroidectomy (non-toxic) ..	2
Appendicectomy	8	Carcinoma of middle ear and block dissection of neck	1
Abdomino-perineal resection of rectum	8	Cystectomy	1
Nephrectomy	7	Laryngectomy	1
Local mastectomy	7	Minor mammary operation ..	1
Open reduction of fracture of femur	6	Removal of nodule of tongue	1
Pancreatectomy	6	Removal of parotid tumour ..	1
Laparotomy	5	Sympathectomy	1

Thoracic Surgical Cases.—Guedel and Treweek (1934) and Nosworthy (1941) established controlled respiration to provide greater safety for thoracotomy. They induced apnoea by deep anaesthesia aided by hyperventilation of the lungs. Present-day methods employ light nitrous oxide anaesthesia with a muscle relaxant to produce apnoea, thereby avoiding deep anaesthesia. However, some muscle relaxants, for instance, D-tubocurarine, are reported to produce excessive bleeding, and in cases where haemorrhage should be carefully avoided it is preferable that they should not be used. In the series of thoracic surgical cases reported, dipipanone in sufficient dosage, combined with hyperventilation, was used to produce apnoea. Following intubation under thiopentone and suxamethonium, and, if necessary, the insertion of an endobronchial blocker or tube, apnoea was induced with an intravenous injection of dipipanone aided by hyperventilation. Anaesthesia was then maintained with nitrous oxide and oxygen, with the occasional addition of 2.5 to 5 mg. of dipipanone intravenously.

Results in Obstetric Cases

In the series of obstetric cases dipipanone was found to be a perfectly satisfactory analgesic for use in labour (see Table III). Only in the occasional case was supplementation with nitrous oxide and air required in the second stage. The doses used, the times of administration, and the results obtained are given in detail in Table IV.

In many cases 25 mg. of dipipanone appeared to produce better analgesia than 100 mg. of pethidine. This was particularly so in the early stages of labour in those cases in which there was a large baby or where the foetal head had presented in the occipito-posterior position. Where adequate

analgesia could not be produced with dipipanone, morphine and pethidine also failed. The midwives formed the impression that dipipanone speeded up labour relative to pethidine and that relaxation between the contractions was better.

TABLE IV.—Dipipanone: Details of 53 Obstetric Cases

Case No.	Dose	Time from Administration of Dipipanone to Full Dilatation		Time from Full Dilatation to Delivery		Degree of Analgesia	Comment
		Hrs.	Mins.	Hrs.	Mins.		
1	25 mg.	6	45	0	25	Adequate	
2	25 "	2	0	0	30	"	
3	25 " repeated after 6 hrs., repeated after 4 hrs.	11	5	0	9	Moderate	Also received morphine 1/6 gr. and hyoscine 1/150 gr. Infant required 1 mg. N-allylnormorphine
4	25 mg.	8	30	0	15	Adequate	
5	25 "	11	45	0	17	"	
6	25 "	2	15	0	30	"	
7	25 "	0	25	0	15	"	Dipipanone appeared to shorten second stage of labour
8	25 "	0	15	0	13	"	
9	25 "	1	55	2	10	"	
10	25 "	3	20	0	45	"	
11	25 " repeated after 4 hrs.	4	40	0	15	Moderate	
12	25 mg., repeated after 3 hrs.	3	25	2	0	"	
13	25 mg.	1	15	0	20	Adequate	Dipipanone appeared to shorten second stage of labour
14	25 mg.	4	0	2	0	"	
15	25 " repeated after 6 hrs.	6	35	0	25	"	
16	25 mg., repeated after 3 hrs.	11	15	0	25	"	
17	25 mg.	1	30	0	30	"	Dipipanone appeared to shorten second stage of labour
18	25 " repeated after 4 hrs.	5	0	0	30	Moderate	
19	25 mg.	11	50	0	30	Adequate	
20	25 "	1	0	0	20	"	
21	25 "	0	45	0	20	"	
22	25 "	3	30	0	35	"	
23	25 " repeated after 6 hrs.	13	10	2	20	"	
24	25 mg.	1	20	0	35	"	
25	25 "	2	30	3	5	"	
26	25 "	3	55	1	5	"	
27	25 "	1	0	0	35	"	
28	25 " repeated after 5 hrs.	6	0	2	30	"	
29	25 mg., repeated after 4 hrs.	10	55	1	0	"	
30	25 mg.	3	0	0	55	"	
31	25 "	3	0	0	25	"	
32	25 "	0	30	1	15	"	
33	25 "	2	55	1	5	"	
34	25 "	4	15	0	25	"	
35	25 "	1	10	0	30	"	
36	25 " repeated after 8 hrs.	13	15	2	45	"	
37	25 mg.	4	30	1	15	"	
38	25 "	2	10	0	50	"	
39	25 "	0	40	1	5	"	
40	25 "	1	55	1	30	"	
41	25 "	3	34	0	55	"	
42	25 " repeated after 11 hrs., repeated after 5 hrs.	16	55	0	45	Moderate	Also received morphine 1/6 gr., hyoscine 1/150 gr., and pethidine 100 mg. Infant required 1 mg. N-allylnormorphine
43	25 mg.	4	50	1	0	Adequate	
44	25 "	0	30	0	55	"	Dipipanone appeared to shorten second stage of labour
45	25 "	4	10	0	25	"	
46	25 "	1	5	0	35	"	
47	25 "	0	5	0	0	"	
48	25 "	1	5	1	20	"	
49	25 "	2	20	0	40	"	
50	25 "	1	20	0	45	"	
51	25 "	1	0	0	35	"	
52	25 "	21	0	2	10	"	
53	25 "	2	45	2	30	"	

TABLE III.—Obstetric Cases: Pain Relief with Dipipanone and Pethidine

	Dipipanone	Pethidine
Adequate relief	48	47
Moderate "	5	5
Little or no "	0	1
Total	53	53

Statistical analysis, however, showed that the duration of the various stages of labour was significantly the same with dipipanone as with pethidine (Table V). Dipipanone tended

TABLE V.—*Obstetric Cases: Duration of Labour*

	Mean Time from Administration of Analgesic to Full Dilatation	Mean Time from Full Dilatation to Delivery	Mean Time from Administration of Analgesic to Delivery
Pethidine ..	4 hrs. 52 mins. ± 46 mins.*	39 mins. ± 11 mins.*	5 hrs. 30 mins.
Dipipanone	4 hrs. 32 mins. ± 38 mins.*	56 mins. ± 6 mins.*	5 hrs. 29 mins.

* Standard error of the mean.

to produce analgesia of longer duration than pethidine and required less supplementation in the second stage.

Depression of foetal respiration was noted in three cases in which dipipanone was used and in four cases with pethidine. Of the three cases, one had received morphine and hyoscine before being given dipipanone, and the infant was successfully treated by the injection of 1 mg. of N-allylnormorphine. The second case had not only received morphine and hyoscine but pethidine in addition to the dipipanone, and this infant also was successfully treated with N-allylnormorphine. In the third case respiratory depression had been caused by a tight cord around the foetal neck. Of the four infants which had respiratory depression following pethidine, two required an injection of N-allylnormorphine.

Results in General Surgical Cases

In the general surgical cases the full analgesic and respiratory effects developed in from five to ten minutes. The degree of analgesia obtained was adequate, and only seldom was reinforcement with trichlorethylene necessary, and that for but brief periods. The duration of the operations performed varied from 15 to 68 minutes. The total dose of dipipanone required tended to rise with increase in the

FIG. 1.—Graph showing variation of total dose of dipipanone with length of operation.

FIG. 2.—Graph showing variation of total dose of dipipanone with patients' body weight.

duration of operation, but there was wide variation (Fig. 1). Likewise the total dose of dipipanone required tended to rise with increase in the patient's body weight (Fig. 2). The average total dose lay in the region of 5 to 10 mg. of dipipanone, although in isolated cases as much as 25 mg. in divided doses was required. In our series of cases anaesthesia was smooth, and reflex disturbances were notably absent. In this respect our results appear to differ from those reported by Masson (1956).

Results in Thoracic Surgical Cases

In the thoracic surgical cases the combined use of dipipanone and hyperventilation allowed a state of apnoea to be maintained with almost no side-effects. Unlike pethidine, the drug appeared to have little effect on the blood pressure or pulse rate. Once closure of the thoracic wall had begun, carbon dioxide absorption was discontinued and full respiratory volume was generally re-established by the end of the operation. In those cases in which the respiration was still depressed, 1 to 5 mg. of N-allylnormorphine sufficed to restore it. Both the respiratory and analgesic effects of dipipanone were reversed and the patient regained consciousness with a sufficient cough reflex. In our experience N-allylnormorphine was rarely needed if the final dose of dipipanone was carefully judged and timed. Bronchospasm did not occur provided there was a smooth transition from the action of suxamethonium to that of dipipanone.

With this technique the use of relaxants could be completely avoided during thoracotomy. In addition, the undesirable side-effects of neostigmine could be avoided, particularly those of bronchospasm and bradycardia after the patient had been returned to the ward and was under the care of the nursing staff.

Discussion

The principal difference between dipipanone and pethidine as an analgesic in labour is the much smaller hypnotic effect of the former. This allows the mother to obtain good relief of pain yet remain fully awake and co-operative. Although the patient in severe pain may fall asleep after dipipanone, this is thought to be largely due to fatigue and relief from pain. Dipipanone appears to have a definite place in obstetrics, and further investigation may well put it on a par with pethidine in this field.

In general surgery, dipipanone is capable of adequately supplementing nitrous oxide anaesthesia. For intra-abdominal surgery needing controlled respiration we have used dipipanone with small quantities of suxamethonium in a 1% solution intravenously. This has enabled us to use the relaxant for the initial opening of the peritoneum and its closure, using only minimal quantities of the relaxant during the operation itself. Following thiopentone induction in adequately premedicated patients of 8 to 10 stone (51–63.5 kg.) undergoing surgery, we found an initial dose of 2.5 to 5 mg. of dipipanone to be adequate. A dose of 10 mg. of the drug given intravenously may produce marked respiratory depression and larger doses respiratory arrest, yet in the conscious unpremedicated patient 25 mg. intramuscularly causes no obvious respiratory depression. Dipipanone produces only minor falls in blood pressure in contrast to pethidine, which after thiopentone induction can produce a fall to as low as 55 mm. systolic pressure (Lancaster and Levin, 1956).

The achievement of apnoea in thoracic surgery without the use of muscle relaxants appears to us to have certain advantages, particularly in such operations as thymectomy for myasthenia gravis, where relaxants are contraindicated.

Summary

The use of dipipanone hydrochloride as an adjuvant to nitrous oxide and oxygen anaesthesia and as an analgesic for the relief of pain in labour has been investi-

gated over a period of 18 months. With 25 mg. of dipipanone given by the deep subcutaneous or intramuscular route, adequate relief of pain in labour was achieved in over 90% of cases. Dipipanone was found to be a satisfactory adjunct to general anaesthesia. The dose initially required varied from 2.5 to 5 mg. according to the patient's age, weight, and physical condition. The total dose required for an operation of average duration was from 5 to 10 mg.

An alternative technique for the maintenance of controlled respiration during thoracotomy is presented, using dipipanone in place of muscle relaxants.

We wish to thank Mr. Kirwan Taylor for permission to conduct the trial of dipipanone in his maternity unit and to Sister Styles and her staff for their co-operation and help. We should also like to express our appreciation of the help we received from Sister Mathias, the senior theatre sister. We owe a special debt to Dr. G. Edwards for his encouragement and advice. "Pipadone" brand injection of dipipanone hydrochloride was kindly supplied by Burroughs Wellcome and Co.

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BUTHALITONE SODIUM IN OUT-PATIENT ANAESTHESIA

BY

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Buthalitone sodium, a short-acting thiobarbiturate, was first described by Miller *et al.* (1936). Following reports by Weese and Koss (1954) on its pharmacology and clinical use, it has been marketed as "transithal," "ulbreval," "baytenal," and thialbutone. Weese and Koss report on its use in 350 cases, both alone and combined with other anaesthetic agents. Similarly, Davidson and Love (1956) describe a series of 200 cases, the majority of which had buthalitone alone as a single dose. In both series an unspecified proportion of cases were out-patients, although in Davidson and Love's they constituted the largest group. Previously Nobes (1955b) had reported that if buthalitone is used for induction only and nitrous oxide and oxygen used for maintenance "a smooth and rapid recovery can be predicted far more confidently than with other intravenous agents used in the same way." No data were given in support of this statement, and the present paper describes an investigation into this technique of using buthalitone in 150 out-patients. Two other small series of cases are also included, illustrating the use of this drug in younger children and in out-patients where intubation was required.

Pharmacology

Buthalitone sodium is the sodium salt of 5-allyl-5-iso-butyl-2-thiobarbituric acid, having the formula:

Like other thiobarbiturates, it is a yellow powder readily soluble in water. However, the solution is readily decomposed by atmospheric carbon dioxide and must always be freshly prepared before use. In the preparation used (transithal), 6% by weight of anhydrous sodium carbonate had been added to inhibit this decomposition, the pH of the resulting 10% solution being about 10.5. This is approximately the same as that of a 5% solution of thiopentone. Therefore a 10% solution of buthalitone is probably as irritant to tissues as a 5% solution of thiopentone. This has, in fact, been demonstrated by Davidson and Love (1956), who record two instances of extravenous injection. Similarly, intra-arterial injection would probably involve the same risk as that of thiopentone.

From their experiments with intravenous buthalitone in dogs, Weese and Koss (1954) report a transient and slight fall in blood pressure, but no cardiac irregularities were observed. The first sign of overdosage was depression of the respiratory centre. Detoxification was shown to take place in the liver, but a small proportion could be recovered from the urine.

Series A: Method of Investigation

This group comprised 150 out-patients aged 10 years and over, the oldest being 82 years. The average age was 31.1 years. These patients were unselected and the trial was conducted with a view to finding whether the use of buthalitone would prove more satisfactory in out-patient anaesthesia than existing inhalational techniques. The main requirements were avoidance of hypoxia during maintenance and rapid recovery from the anaesthetic in order to allow early ambulation. The need for an anaesthetic of this nature was accentuated by the fact that most of the patients were attending a special hand unit, where the surgical techniques employed demanded a longer operating time than is customary in most casualty departments. Another advantage would seem to be a more rapid and pleasant induction of anaesthesia for the patient.

The use of buthalitone alone in a single-dose technique was rejected because it was felt that, if sufficient dosage was to be given in order to ensure adequate anaesthesia to meet surgical requirements (up to 10 minutes in most cases), respiratory depression deep enough to require artificial respiration would be produced in many instances; buthalitone, like other thiobarbiturates, being only a hypnotic and not primarily an anaesthetic agent. Intermittent dosage of buthalitone was also rejected because it was considered that there would be a danger of prolonging the recovery time, as was in fact observed by Davidson and Love (1956). Therefore a single dose of buthalitone was followed by maintenance with nitrous oxide and oxygen. This method was adopted because it was felt that a more flexible anaesthesia would be produced which would satisfy our requirements as stated above.

Most of the patients were healthy young adults, but three had diabetes mellitus, two had chronic bronchitis, one had bronchiectasis, and one had well-compensated mitral stenosis.

Operations were performed for the following conditions: septic hands, 77 cases; other septic lesions, 25; removal of toenails, 13; manipulation of fractures, 21; miscellaneous, 14.