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RELIEF OF POST-OPERATIVE PAIN

BY

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Relief of pain following major surgery is necessary for two main reasons: (1) the patient's general comfort; and (2) to enable limb, trunk, and breathing exercises designed to prevent post-operative complications, particularly thrombosis and embolism, to be carried out satisfactorily. In an endeavour to find the best available means of relieving post-operative pain a study was made of three recently introduced analgesics—dihydrocodeine, dipipanone, and dextromoramide (R 875)—to determine if these offered any advantage over conventional analgesics, such as morphine.

Chemistry and Pharmacology

Dihydrocodeine, a close chemical analogue of morphine, was first reported to be a potent analgesic in the experimental animal by Eddy and Small (1934). Gravenstein *et al.* (1956) showed that 30 mg. of dihydrocodeine was approximately equianalgesic with 10 mg. of morphine, with a slightly shorter duration of action, but with substantially fewer side-effects. These workers found that increasing the dose from 30 to 45 mg. did not appreciably enhance the analgesic effect.

Dipipanone is related chemically to methadone, and its analgesic properties were first described by Ofner *et al.* (1950). Cahal (1957) showed that a dose of 25 mg. raised the pain threshold in man to the same extent as did 10 mg. of morphine. Its use in doses of this order for the relief of pain due to acute and chronic medical conditions and in post-operative pain was reported by Gillhespy *et al.* (1956) and its use as an analgesic in labour by Coleman *et al.* (1957). In these studies adequate relief of pain was obtained in about 95% of cases, with an incidence of side-effects of less than 5%.

Dextromoramide, chemically a new type of analgesic, was synthesized and its analgesic properties first described by Janssen and Jageneau (1957). Although weight for weight twenty times more potent than morphine in the experimental animal, its ability to raise the pain threshold in man was found by Cahal (1958)

to be approximately the same. Its use in the treatment of pain in doses up to 10 mg. was reported by Soupault *et al.* (1957) and by David and Deligné (1957).

The structural formulae of the three analgesics are as follows:

Method and Materials

As papaveretum, the post-operative analgesic already in use by us for a number of years, was reliable, and as its analgesic properties could be attributed to its content of morphine, it was used in preference to morphine itself as the standard with which to compare the other drugs. It was thought that the safest form of trial consistent with a fair comparison of these four potentially dangerous drugs was to treat similar series of post-operative patients with each of them in random order. The number of patients treated, the nature of the operations performed, and the order in which the analgesics were given are shown in Table I. The four

TABLE I.—Details of Cases Treated

Order	Analgesic	Major Gynaecological Surgery	Lower Segment Caesarean Section	Total Cases
1	Papaveretum 20 mg. ..	100	25	125
2	Dipipanone 25 mg. ..	100	25	125
3	Dihydrocodeine 50 mg. ..	40	20	60
4	Dextromoramide 10 mg. ..	55	25	80
	Total ..	295	95	390

series of cases treated were similar with respect to the patients' mean age and weight, the type and duration of operation, the surgical techniques used, and pre-operative and post-operative care.

The dose level chosen for each drug was that which on the basis of the available clinico-pharmacological data would be expected to give a good level of analgesia with minimal side-effects. These were: papaveretum 20 mg., dipipanone 25 mg., dihydrocodeine 50 mg., and dextromoramide 10 mg. These doses were approximately equianalgesic with morphine 10 mg. (1/6 gr.) and the drugs were administered subcutaneously every six hours

for the first 36 hours after operation. Neither the patients receiving the drugs nor the nursing staff assessing pain relief had prior knowledge of the nature of the compounds under investigation.

Objective and subjective assessment of pain relief was made at 15-minute intervals during the first hour after injection and every hour thereafter. Relief of pain was classified broadly as excellent, moderate, slight, or nil. Use of the term "complete relief" (Gillhespy *et al.*, 1956) has now been abandoned by us as inappropriate, for analgesia invariably takes some time to develop and pain gradually reappears after about the fourth or fifth hour.

Results

Pain relief produced by the four drugs under investigation and the incidence of side-effects in relation to the total number of doses given are shown in Tables II and III respectively. No important differences were observed to occur between the series of post-operative gynaecological cases and those which had undergone caesarean section. Therefore the figures for the two types of case have been combined.

TABLE II.—*Relief of Post-operative Pain by Subcutaneous Injection*

Analgesia	Papaveretum 20 mg.	Dipipanone 25 mg.	Dihydro- codeine 50 mg.	Dextromor- amide 10 mg.
Excellent ..	115 (92%)	114 (91.2%)	21 (35.0%)	67 (83.8%)
Moderate ..	10 (8%)	10 (8.0%)	34 (56.7%)	11 (13.7%)
Slight ..	0	1 (0.8%)	5 (8.3%)	2 (2.5%)
Nil ..	0	0	0	0
Total ..	125	125	60	80

TABLE III.—*Side-effects after Subcutaneous Injections*

Side-effects	Papa- veretum 20 mg.	Dipipanone 25 mg.	Dihydro- codeine 50 mg.	Dextromor- amide 10 mg.
Sweating ..	22 (3.0%)	28 (3.7%)	10 (2.9%)	37 (8.2%)
Giddiness ..	14 (1.9%)	13 (1.7%)	5 (1.4%)	201 (44.2%)
Nausea only ..	4 (0.5%)	6 (0.8%)	0	0
Nausea and vomiting	25 (3.4%)	6 (0.8%)	12 (3.5%)	25 (5.5%)
Headache ..	0	1 (0.1%)	96 (27.6%)	9 (1.9%)
Apnoea with uncon- sciousness ..	0	0	0	3 (0.7%)
Total side-effects ..	65 (8.8%)	54 (7.1%)	123 (35.4%)	275 (60.5%)
Total No. of doses ..	732	750	348	455
No. of patients ..	125	125	60	80

When administered subcutaneously there was no significant difference between the analgesics in the time of onset of analgesia or in its duration of action. Slight relief occurred in each instance in 10 minutes and maximum relief in about 20 minutes. After four and a half to five hours pain gradually returned, and increased in intensity until at six hours a further dose of analgesic became necessary. Marked differences existed, however,

TABLE IV.—*Comparison of Pairs of Analgesics with Respect to Analgesia and Side-effects*

	Best Analgesic Effect	Lowest Incidence of Side-effects
Papaveretum and dihydrocodeine ..	Papaveretum. P<0.05	Papaveretum. P<0.05
" dipipanone ..	No sign. diff.	No sign. diff.
" dextromoramide ..	" "	Papaveretum. P<0.05
Dihydrocodeine and dextromoramide	Dextromor- amide. P<0.05	No sign. diff.
" dipipanone ..	Dipipanone. P<0.05	Dipipanone. P<0.05
Dipipanone and dextromoramide ..	No. sign. diff.	Dipipanone. P<0.05

in the level of analgesia achieved and in the total incidence of undesirable side-effects. The significance of the differences between the various pairs of analgesics is shown in Table IV.

Sedation—sometimes a desirable and sometimes an undesirable property of an analgesic but difficult to distinguish reliably from the effects of pain relief—was judged mainly by the patient's ability to get off to sleep at night without the use of a hypnotic. Dipipanone 25 mg. and dihydrocodeine 50 mg. did not induce sleep, although the latter produced drowsiness in some cases, and had to be supplemented at night with amylobarbitone sodium 3 gr. (0.2 g.). Adequate sleep was induced both with papaveretum 20 mg. and dextromoramide 10 mg., and amylobarbitone sodium was not required.

Severe respiratory depression amounting to apnoea occurred in three cases receiving dextromoramide. After the first of these the dose of this analgesic was reduced from 10 to 7.5 mg., and when two further cases occurred in rapid succession its use as a post-operative analgesic was discontinued. The details of these three cases were:

Case 1.—A woman aged 49 had undergone a total hysterectomy for uterine fibroids and appendicectomy. Before operation her general health had been good and there was no history of allergic disease or drug sensitivity. Post-operatively her condition was satisfactory, and dextromoramide, 10 mg. subcutaneously, was given six-hourly to relieve pain. The analgesia was good and the patient slept for two to two and a half hours following each injection. Twenty minutes after the fifth injection her respiration was seriously depressed and she became apnoeic and unconscious. Her blood pressure was normal (120/80) and her pulse rate 70 and regular. Continuous oxygen was immediately administered and resuscitation measures were instituted. Nalorphine was temporarily withheld, but intravenous nikethamide 1 ml. and aminophylline 500 mg. were given. Within five minutes respiration restarted spontaneously. The patient was fully conscious after 30 minutes and completely recovered in one hour.

Case 2.—A healthy woman of 39 underwent a Manchester type pelvic floor repair operation for prolapse. Five hours after the operation, when she had fully recovered from the anaesthetic and was in good general condition, 7.5 mg. of dextromoramide was given subcutaneously. Ten minutes later there was slight relief of pain and she was awake and well. Twenty minutes after the injection she was unconscious and apnoeic. The pulse was just palpable and the rate 70 and regular. She was pale but not cyanosed; the skin was warm and there was no excessive perspiration. She was lowered from the Fowler position and the foot of the bed was raised. Continuous oxygen was administered and resuscitation carried out. Nalorphine was withheld, but nikethamide 2 ml. was given intravenously and was quickly followed by a spontaneous return of respiration. This was slow at first but adequate after 10 minutes. Full consciousness was regained after 30 minutes, and in 45 minutes she was comfortable and co-operative, but felt drowsy.

Case 3.—A healthy woman aged 70 who had undergone a Manchester type pelvic floor repair operation was given 7.5 mg. of dextromoramide subcutaneously five and a half hours later. She appeared to have recovered completely from the anaesthetic and her general condition was good. Ten minutes after the injection she had slight relief of pain. After 20 minutes there was moderate relief of pain, she was very drowsy, her pulse rate was 80, and there was no undue respiratory depression. Thirty-five minutes after the injection her respiratory rate fell to 6 a minute and she became unconscious. Her pulse rate was 110–120 and blood pressure 180/110. She did not become apnoeic. In a few

minutes her respiratory rate increased and in 10 minutes she recovered consciousness. She remained drowsy for three hours, but was quite co-operative when aroused.

In this series of 390 cases there was only one death which was attributable to post-operative complications.

A coloured woman aged 37 with a bulky fixed retroverted uterus bound down in the pouch of Douglas by numerous adhesions distorting the Fallopian tubes. At operation the adhesions were divided, the tubes were rendered patent, and the uterus was fixed by means of a Gilliam suspension. Post-operatively dihydrocodeine, 50 mg. six-hourly, was given and provided moderate relief of pain. However, she was apprehensive and reluctant to carry out her exercises. Although she had been ambulant from the second post-operative day and had seemed well, she suddenly had a massive pulmonary embolism on the eighth day. There were no warning symptoms or signs, and she died in 20 minutes.

Discussion

Intravascular thrombosis, with the possible sequel of pulmonary embolism, is perhaps the greatest danger to the post-operative patient now that wide and more rational use of blood transfusion and modern developments in chemotherapy have minimized the danger from other complications (Bourne and Williams, 1953). Statistical figures show a great variation, but at present pulmonary embolism accounts for 15% of all post-operative deaths, and probably 0.25% of patients submitted to gynaecological operations die from this cause (Shaw, 1954). Although thrombosis and embolism do not usually manifest themselves until the eighth to the twelfth post-operative day, it is probable that thrombosis starts in the immediate post-operative period, when the circulating thrombokinasase is at a maximum and the patient is least mobile.

While opinion on this point is not unanimous it would seem that one of the best safeguards against such a catastrophe is to teach the patient limb, trunk, and breathing exercises prior to operation and to continue these as soon as he is sufficiently recovered from the anaesthetic. Early ambulation is also said to reduce the incidence of post-operative pulmonary embolism (Shaw, 1954). With these methods the number of deaths from post-operative pulmonary embolism has been 1 in the series of 390 cases reported in this paper and 3 in the last 1,700 major gynaecological operations performed by one of us (E. C.), an incidence of less than 0.2%.

To obtain the necessary co-operation from the patient adequate pain relief without drowsiness, respiratory depression, or side-effects such as giddiness, nausea, and vomiting is essential. Persistent vomiting is thought to be particularly undesirable, for this causes dehydration, with increased haemoconcentration and a greater liability to thrombosis.

The order in which the four drugs investigated satisfied the criteria of a good post-operative analgesic were: dipipanone, papaveretum, dextromoramide, dihydrocodeine. Papaveretum and dipipanone both produced excellent relief from pain and a low incidence of side-effects. The former, however, produced sleep in 116 out of 125 patients following the first three doses, and in many cases the patients were too drowsy on the day following operation to co-operate fully in the performance of exercises. Apart from this, vomiting was the only important side-effect of papaveretum, although in only about one-half of the instances reported could this be definitely ascribed to the drug. Giddiness with both papaveretum and dipipanone, when it

occurred, did so on the second post-operative day, when the patients tended to be in a more upright position.

Dextromoramide, while affording good analgesia, produced a high incidence of side-effects, in particular giddiness, sweating, and respiratory depression. In the three cases here reported the period elapsing between injection and the onset of respiratory depression excludes the possibility that the drug may accidentally have entered a vein. Although it can readily be fully reversed with nalorphine (Janssen and Jageneau, 1957; A. F. Green, 1958, personal communication) severe respiratory depression amounting to apnoea following the subcutaneous administration of an analgesic must be regarded as a disadvantage.

As a result of previous experience with dihydrocodeine 30 mg., the dose level used in this investigation was raised to 50 mg. Even so, its analgesic effect was significantly less than that of the other drugs. Increasing the dose from 30 to 50 mg. did not appear substantially to enhance the analgesic response, and in this respect our findings agree with those of Gravenstein *et al.* (1956).

It was not possible in this investigation to make a reliable study of side-effects, such as constipation and addiction, which arise during long-term administration and which may be of considerable importance when the drugs are used for the relief of chronic pain.

Summary

In an endeavour to find the best available analgesic for the control of post-operative pain a study was made of three recently introduced analgesics—dipipanone, dihydrocodeine, and dextromoramide—to determine if these offered any advantage over conventional analgesics based on morphine.

The order in which the four drugs investigated satisfied the criteria of a good post-operative analgesic were: dipipanone 25 mg., papaveretum 20 mg., dextromoramide 10 mg., and dihydrocodeine 50 mg. The importance of adequate pain relief in the immediate post-operative period and its possible effect on the incidence of thrombo-embolism are discussed.

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