DIPIPANONE HYDROCHLORIDE IN THE TREATMENT OF SEVERE PAIN

A REPORT OF 200 CASES

BY

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The need for a potent analgesic which is non-habit-forming, quick but long-acting, and free from undesirable side-effects has become more pressing recently owing to the possible ban on the manufacture of heroin. Morphine and its substitutes in common use, though satisfactory in many instances, often produce undue toxic side-effects and, if administered over a prolonged period, tend to cause addiction. In our experience morphine frequently causes nausea and vomiting, particularly in women, whilst methadone and pethidine tend to be less certain in their action than morphine, have similar side-effects, and both may give rise to drug addiction. We therefore decided to give dipipanone hydrochloride an extensive trial to find out if the objections to the other analgesics had been overcome in this compound.

Chemistry and Pharmacology

Dipipanone, or DL-6-piperidino-4:4-diphenyl-heptan-3-one, is closely related chemically to methadone ("physeptone").

This compound was first mentioned by Ofner, Thorp, and Walton (1949), and its synthesis was originally described, with a note on its analgesic action in rats and dogs, by Ofner, Walton, Green, and White (1950). A test of its analgesic activity in the rat was described by Green and Young (1951). Its use as an adjunct to general anaesthesia, under the code number 379C48, has been reported on by Masson (1956).

In experimental animals the pain threshold is raised by an effective dose of dipipanone to an extent fully comparable with that obtained with morphine. In the rat the analgesic activity is approximately two and a half times that of morphine (Ofner *et al.*, 1950) and the duration of activity is about the same. The respiratory depressant effect of di-

pipanone has been reported to be less than that of an equi-analgesic dose of morphine (Ofner *et al.*, 1949). Both drugs reduce the respiratory minute volume mainly by slowing respiration. Given subcutaneously, the temperature-lowering activity of dipipanone is roughly proportional to its analgesic activity. Recovery, however, is more rapid than after morphine. The acute toxicity of dipipanone is approximately the same as that of methadone (intravenously in mice LD50=20 mg. per kg.; subcutaneously in rats LD50=80-120 mg. per kg.). Signs of overdosage in dogs closely resemble those occurring with morphine; there is usually constriction of the pupil and sometimes salivation, defaecation, and vomiting, the incidence and severity of which are less than with morphine. The mechanism of the action on the bowel is probably the same as that of other morphine-like analgesics, as it abolishes the stretch reflex of isolated guinea-pig ileum. While its main toxic action is on respiration, intravenous doses of 5 mg. or more per kg. reduce the tone of cardiac muscle.

Dipipanone has some atropine-like properties. In relaxing carbachol-induced spasm of isolated rabbit ileum, it has one-fortieth the activity of atropine sulphate and three times that of methadone. Histamine-induced spasm of isolated guinea-pig ileum is relieved only by very high concentrations, and the activity of dipipanone in this respect is only about one-five-hundredth that of mepyramine. Its atropine-like action probably accounts for its mydriatic effect in mice, in which it is one-fiftieth as active as atropine when given intraperitoneally.

Nalorphine antagonizes the analgesic and respiratory actions of dipipanone. The effective dose is approximately the same as that required to antagonize an equi-analgesic dose of morphine. The deep narcosis and severe respiratory depression produced in dogs by intravenous injection of 5 mg. or more of dipipanone per kg. can be completely reversed by injecting, preferably intravenously, 2-5 mg. of nalorphine per kg.

Daily subcutaneous injection into newly weaned rats of twice the effective analgesic dose for a period of 10 weeks produced no change in the red-cell count or in the histological appearances of the lung, liver, spleen, or kidney.

Selection of Patients

It was thought that the appraisal of dipipanone would be more accurate if patients suffering from pain due both to natural disease and to operative intervention were included in the trial. The analgesic was therefore given to two distinct groups of adult patients: (1) a series of 100 consecutive cases admitted to the medical wards and suffering from pain which could not be relieved without the use of a potent analgesic (R. O. G.); and (2) a series of 100 cases which had undergone major gynaecological operations (E. C.).

Before administration of the analgesic, the intensity of the pain in the medical cases was very severe in 73, severe in 3, and moderate in 24 cases. Sixty-four cases would normally have been given morphine and the other 36 methadone or pethidine. The conditions primarily responsible for the pain in this series are shown in Table I.

It is well known that gynaecological operations give rise to severe post-operative pain and are accompanied by a higher than normal incidence of thrombo-embolism. Although thrombosis and embolism do not usually manifest themselves until several days after the operation, it is probable that thrombosis starts in the immediate post-operative period, when circulating thrombokinase is at a maximum and the patient is least mobile. A good circulation in the legs in the first few post-operative days depends upon adequate function of both the leg and thoracic venous pumps. This, in turn, depends upon the achievement of good pain relief without drowsiness or depression of respiration, so that the patient can undertake sufficient limb, trunk, and breathing exercises without undue discomfort. Patients who had undergone major gynaecological surgery were therefore

TABLE I.—Cause of Pain in 100 Medical Patients

Cause of Pain	No. of Cases
Pleurisy (mainly diaphragmatic)	29
Coronary thrombosis	23
Meningitis	6
Subarachnoid haemorrhage	5
Paget's disease with bone pain	5
Malignant disease	5
Peptic ulcer	4
Pericarditis	3
Sciatica	3
Renal colic	3
Gangrene of the foot	2
Arthritis of the spine	2
Severe rheumatoid arthritis	2
Pulmonary infarction	1
Biliary colic	1
Cholecystitis	1
Parkinsonism (cramp-pain and rigidity)	1
Ulcerated leg	1
Frontal sinusitis	1
Painful distension due to abdominal ascites	1
Painful obstruction of the bowel	1

thought to be particularly suitable for the purposes of the trial, and the nature of the operations performed is shown in Table II.

TABLE II.—Nature of Gynaecological Operations Performed in 100 Cases

Operation Performed	No. of Cases
Total hysterectomy (including two Wertheim operations)	32
Pelvic floor repair (Manchester type)	24
Vaginal hysterectomy	5
Lower segment caesarean section	18
Other gynaecological abdominal operations: myomectomy, ovariectomy, ectopic pregnancy, etc.	21

Design and Organization of the Trial

During a period of approximately six months all patients suffering from pain severe enough to need a potent analgesic, admitted to or already in the medical wards of one of us (R. O. G.), were treated with dipipanone. One hundred consecutive patients who had undergone major gynaecological surgery were likewise treated (E. C.).

Each administration of analgesic was recorded by the sister in charge of the ward on a form specially designed for the purpose. A record was also made of the initial intensity of pain, its apparent cause, its duration, and of any other drug being given concurrently with dipipanone. At intervals after the administration of dipipanone, the degree of the relief of pain, the degree of hypnosis, and the presence or absence of side-effects were noted and recorded. Relief of pain was classified as "complete," "moderate," "slight," or "nil." Hypnotic effect was classified as "asleep," "very drowsy," "slightly drowsy," or "nil." For the convenience of the nursing staff a list of side-effects common to potent analgesics was included on the form. Observations were continued for a period of eight hours after each administration and the forms were checked by our assistants and ourselves on routine ward rounds. At the end of the trial an independent breakdown of results was performed in both groups.

Dosage and Method of Administration

Before the beginning of the trial the optimal dose of dipipanone was determined for each of the two groups of cases. A dose of 25 mg. given subcutaneously to a small number of medical cases produced occasional nausea, vomiting, sweating, giddiness, and headache. Reduction of the dose to 20 mg. virtually abolished the incidence of side-effects, and this was the dose given to the medical cases in the trial. Patients with post-operative pain were better able to tolerate 25 mg., and this was the dose given to the surgical cases.

In all cases the drug was given subcutaneously. This route of administration was found to be entirely satisfactory and no local reaction or pain at the site of injection occurred. In the medical cases with persistent pain the drug was given eight-hourly, but in the post-operative cases six-hourly administration was found to be necessary.

During the trial period 100 acute and chronic medical cases received a total of 803 injections of dipipanone. The

maximum number of injections given to any one patient was 80 and the average number of injections per patient was eight. In most cases the condition responsible for the pain rapidly responded to therapy, and analgesia was no longer necessary. The post-operative cases were given dipipanone six-hourly for the first 48 hours immediately following operation—a total of 800 injections.

Results

Degree of Analgesia.—The degree of pain relief obtained in the medical cases is shown in Table III and that in the cases subjected to surgery in Table IV. In 94 out of 100 medical cases the relief of pain was complete or adequate. In only three cases was transfer necessary to another analgesic—in this instance, morphine; two of these because of

TABLE III.—Pain Relief with 20 mg. of Dipipanone Hydrochloride in 100 Medical Cases

Degree of Pain Relief:	No. of Cases
Complete	67
Moderate	27
Slight	3
Nil	3

TABLE IV.—Pain Relief with 25 mg. of Dipipanone Hydrochloride in 100 Post-operative Cases

Degree of Relief	Total Hysterectomy	Pelvic Floor Repair	Vaginal Hysterectomy	Caesarean Section	Others	Total
Complete	31	24	4	15	21	95
Moderate	1	—	1	2	—	4
Slight	—	—	—	1	—	1
Nil	—	—	—	—	—	0

inadequate analgesia at the 20-mg. dose level and the other because of intolerance to dipipanone. All the post-operative cases obtained some degree of pain relief. In 95 cases out of 100 complete relief was obtained, in four moderate relief, and in one case only slight relief. Three of the five cases showing less than complete relief of pain were non-English-speaking patients who had undergone caesarean section. All three were very apprehensive and at no time did they appear to be in any great pain. However, they indicated that they had some discomfort; in one case up to the seventh day.

Onset and Duration of Analgesia.—In all the cases which responded the onset of analgesia was rapid. In the post-operative patients some relief was obtained within 10 minutes in all cases and maximal analgesia was reached within 20 minutes. In the medical cases, in which the pain was of wider aetiology, the onset of action was also rapid, but the time taken to reach maximal effect was more varied. In cases showing the lower degrees of pain relief it was somewhat difficult to determine when the maximal analgesic effect had been reached, but in most cases this occurred within half an hour. An adequate level of pain relief lasted about five hours in most cases.

Side-effects.—In relation to the number of injections given, the incidence of side-effects was low. These are shown in Tables V and VI. In the medical cases, only on 35 occasions in 803 consecutive injections, or 4%, did an undesirable side-effect occur, and in only one case was this severe enough to justify discontinuance of the drug. In the post-operative cases the incidence of side-effects was 5%. Since these did not persist after the first 24 hours and did not follow administration of the analgesic in the second 24 hours, they were more likely due to the operation or anaesthetic than to dipipanone. The one patient who had headache continued to complain for 10 days. Since the headache persisted long after the analgesic was stopped, it could not reasonably have been due to this drug.

The impression was formed that in the relief of post-operative pain following major gynaecological surgery, dipipanone hydrochloride, 25 mg. subcutaneously six-hourly, was more effective than other analgesics previously used—namely, pethidine 100 mg., morphine $\frac{1}{2}$ gr. (11 mg.), papa-

TABLE V.—*Medical Cases: Incidence of Side-effects Following a Total of 803 Injections*

Vomiting	9
Sweating	8
Nausea	7
Headache	5
Giddiness	5
Blurring of vision	1
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TABLE VI.—*Post-operative Cases: Incidence of Side-effects Following a Total of 800 Injections*

	Total Hyster- ectomy	Pelvic Floor Repair	Vaginal Hyster- ectomy	Caesar- ean Section	Others	Total
Sweating ..	7	8	2	—	4	21
Giddiness ..	2	2	1	4	1	10
Nausea ..	1	2	—	—	1	4
Vomiting ..	2	—	—	2	—	4
Headache ..	1	—	—	—	—	1
Total ..	13	12	3	6	6	40

veretum ("omnophon") $\frac{1}{2}$ gr. (22 mg.), six-hourly. Adequate post-operative analgesia to facilitate early leg and breathing exercises has been found to be especially valuable, and rigorous adherence to this regimen has lowered the incidence of fatal pulmonary embolism to one in the last 1,000 major gynaecological operations performed by one of us (E. C.).

During this trial no obvious respiratory depression or change in blood pressure or pulse rate occurred, nor did any patient complain of anorexia or constipation. In the dosage used, dipipanone appeared to have little hypnotic effect. The post-operative patients were awake and completely co-operative as soon as the anaesthetic had worn off; in fact, amylobarbitone sodium, 3 gr. (0.2 g.), had to be given to some of the patients before they were able to go to sleep.

The blood picture of patients whose blood was examined during the trial showed no change attributable to dipipanone. No withdrawal symptoms were noted after up to 80 effective analgesic doses. However, since in the majority of cases pain was short-lived and prolonged analgesia unnecessary, no conclusion can at present be drawn concerning habit formation with this drug.

Morbidity and Mortality

There were no deaths in the series during the period of the trial. One patient, who had a hysterectomy for fibroids, had a small pulmonary embolism on the fourth day. She was given anticoagulant therapy and made a complete recovery.

Summary

The results of the administration of a new analgesic, dipipanone hydrochloride, to two distinct series, each of 100 cases, are presented. All the cases treated suffered from pain severe enough to justify the use of a potent analgesic.

In the dosage employed, dipipanone was an effective analgesic. Adequate pain relief was obtained in the great majority of cases of post-operative pain following major gynaecological surgery and of pain due to a variety of acute and chronic medical conditions. Only 3 out of the 200 cases treated failed to obtain any relief from this drug. The optimal dose was found to be 20 mg. in the medical cases and 25 mg. in the post-operative cases.

The onset of analgesia after subcutaneous injection occurred within 10 minutes and maximal relief was obtained in about 20 minutes in most cases. The effect lasted for approximately five to six hours. There was no obvious depression of respiration or tendency to drowsiness, nor was there any local reaction or pain at the site of injection.

Side-effects were rare, their incidence in relation to the number of doses administered being 4–5%. The only side-effects of any importance were nausea, vomiting, sweating, and giddiness. In only one case were they severe enough to justify transfer to another analgesic.

Our thanks are due to our assistants and to the sisters in charge of the medical and gynaecological wards at Dudley Road Hospital, Birmingham, without whose co-operation this clinical trial could not have been carried out. The material used in the trial was "pipadone" brand injection of dipipanone hydrochloride, kindly supplied by Burroughs Wellcome and Co.

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N-ACETYL-PARA-AMINOPHENOL AS AN ANALGESIC

A CONTROLLED CLINICAL TRIAL USING THE METHOD OF SEQUENTIAL ANALYSIS

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Acetanilide and phenacetin have long been used for their analgesic and antipyretic properties. Brodie and Axelrod (1948, 1949) have shown that the metabolism in the human body of acetanilide and of phenacetin closely resemble one another in that the major route in each case involves the production of N-acetyl-*p*-aminophenol (N.A.P.A.P.). In each case a high percentage of the ingested drug is excreted by the kidney as conjugated N-acetyl-*p*-aminophenol:

In addition to the major route shown above there is a minor metabolic route which for acetanilide involves the formation of aniline and for phenacetin the formation of *p*-phenetidin. Although neither of these products has been shown to be directly responsible for methaemoglobin formation it is thought that they are both precursors of the methaemoglobin-forming substance. It seems that N.A.P.A.P. is not responsible for