SOME TRIALS WITH 'ORFENSO', A NEW ANALGESIC

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PHARMACOLOGY

Innumerable non-narcotic analgesics are available and, although all are orally active, some are much more toxic than others. There are the salicylates, the aniline derivatives like phenacetin, paracetamol and acetanilide, and the pyrazolone derivatives such as phenylbutazone, phenazone and amidopyrine. To these chemical groups must now be added at least two derivatives of methadone, which are perhaps better described as synthetic analgesics related to methadone. The piperidine ring of 'pethidine'-like drugs can be 'opened' to produce the analgesically weaker derivative of 3-phenyl-butylamine, dextro-propoxyphene. The addition of a phenol ring produces a more potent analgesic, namely, 1-piperidyl-3:3-diphenylketohexane ('orfenso').

Pethidine = C_2H_5OOC-C(/ phenyl radicle) = piperidino with methyl radicles

Dextro-propoxyphene = $(C_6H_5)-CH_2-C(COOC_2H_5)(/\text{phenyl radicle})-CH$ (with methyl radicle) $-CH_2-N(CH_3)_2$

1-piperidyl-3, 3-diphenylketohexane (orfenso) = $(C_6H_5)_2-C(/CH_2-CH_2-\text{piperidino radicle})-CO-CH_2-CH_3$

Methadone = $(C_6H_5)_2-C(/CH_2-CH(/CH_3)-N(CH_3)_2)-CO-C_2H_5$

An examination of the chemical formulae as represented here shows the close relationship between pethidine and piperidinohexanone (orfenso), methadone and dextro-propoxyphene. It is nevertheless of great interest that dextro-propoxyphene is not regarded as a narcotic in the USA, where it can be sold without a prescription, being exempted from the Harrison Narcotic Act. After 5 years of clinical trials in Austria, orfenso was certified a non-narcotic on 5 June 1962 by the Federal Ministry for Social Affairs of the Republic of Austria.

Both orfenso and propoxyphene are actually regarded as closer relatives of methadone than of pethidine, and it is well recognized that methadone, with approximately the same analgesic activity as morphine, produces an abstinence syndrome of about the same intensity as does codeine.[1] Propoxyphene is as effective as codeine,[2] and also as effective as pethidine in doses of 100 mg. given orally every 6 hours for postoperative pain.[3,4] Many of the side-effects that were reported were comparable to those elicited by a placebo. Over a 2-year period no patients have shown a desire for, or need of, an increased dosage, nor was any idiosyncrasy noted.[2]

METHODS AND RESULTS

Methods

An investigation to determine the comparative value of pain-relieving combinations of drugs, as commercially available, was conducted on 205 patients. Most of them had undergone gynaecological operations, and the trial was started in each case 48 hours after operation and continued for 3 days. Four substances were used:

1. Placebo tablets.

2. Orfenso-compound, each tablet containing 0·006G. of piperidyl-diphenylhexanone HCl (orfenso), 0·2 G. of dimethylaminophenyldimethylpyrazolone, 0·3 mg. of benzylic acid—beta dimethylaminoethylbenzylate, 0·3 G. of paracetamol, and 0·03 G. of caffeine.

3. 'Doloxene-compound', a combination of dextro-propoxyphene (32 mg.), acetophenetidin (162 mg.), and acetylsalicylic acid (227 mg.), with caffeine (32·4 mg.).

4. 'Vondar', each capsule of which contained dextro-propoxyphene (32 mg.), acetylsalicylic acid (325 mg.) and phenaglycodol ('ultran'), a tranquillizer (150 mg.).

Observations were made by a sister, a staff-nurse and a medical officer, none of whom had any idea what the different preparations contained, except that they were used for the relief of pain. The placebo tablets looked exactly like the orfenso tablets, and the doloxene and vondar compounds were used in capsule form.

Results

The earliest findings were unwillingness on the part of

the staff to administer the placebo, because it appeared to be quite ineffective, and their firm preference for orfenso. Another early finding was the reluctance of the nursing staff to make use of suppositories; although a large supply of these was left in the ward, mainly containing orfenso, hardly any were used. When oral medication failed, recourse to injections was the rule.

Two patients with advanced, inoperable carcinoma were followed with interest. Only orfenso, in a dose of 2 tablets

TABLE I. PROTOCOLS MADE AVAILABLE TO WARD STAFF TO RECORD THEIR OBSERVATIONS

Johannesburg Hospital—Anaesthetic Department—Analgesics Investigation

Patient ..... Doctor-in-charge ..... Diagnosis .....

Hospital No. ..... Sex ..... Race ..... Age .....

Date ..... Nature of operation .....

Condition before medication:
(State number: 0=well; 1=a little sick; 2=very sick; 4=terribly sick)

Pain intensity:
(0=none; 1=a little; 2=some; 3=a lot; 4=terrible)

Pain relief:
(0=none; 1=a little; 2=some; 3=a lot; 4=complete .... or .... 0=0%; 1=20%; 2=40%; 3=80%; 4=100%)

Other effects from the pills? (Circle if volunteered information): Nausea; vomiting; abdominal discomfort; constipation; diarrhoea; dizziness; drowsiness; headache; itching

How many pills were given? Repeated?

How many suppositories? Repeated?

Was the medication like:

1. Nothing at all?
2. One aspirin?
3. Two A.P.Codein pills?
4. A pethidine or morphine injection?

repeated 6-hourly, proved satisfactory in controlling their severe pain. No habituation or tachyphylaxis became apparent over a period of 2 months.

Table I is a copy of the sheets used for recording the clinical observations, and Table II lists the observations that were recorded.

Three patients vomited, and several felt nauseated after both the doloxene and the vondar combinations of propoxyphene. The exact number is not given, because no side-effects at all were recorded in the series of postoperative gynaecology patients, except the instances of nausea after the capsules; this probably merely reflects the fact that the observers had many other duties to perform, and could not find time to complete the protocols scrupulously. Table II contains the results in some patients in a general surgical ward as well, but more precise documentation than is contained in Table II is not possible, unless special facilities and staff are provided for the express purpose of executing a double-blind, controlled study.

Thirty-seven patients received one suppository only of orfenso for premedication, and 37 alternate patients received pethidine and atropine in appropriate doses. An attempt was made to standardize each anaesthetic by using exactly the same amount of methohexitone ('brietal'),

TABLE II. SOME OF THE RESULTS RECORDED ON FORMS IN TABLE I

Drug given	*Dose*	*No. of administrations*	*Percentage response* %
Placebo	One tablet	4	45
Placebo	Two tablets	21	51·5
Orfenso compound	One tablet	51	78·4
Orfenso compound	Two tablets	114	77·3
Doloxene compound	One capsule	29	59·5
Doloxene compound	Two capsules	33	58·2
Vondar	One capsule	51	63·7
Vondar	Two capsules	69	61·9

namely 100 mg., nitrous oxide and 1·5% halothane, in each case, while allowing spontaneous respiration. Ordinary Nosworthy cards were completed for all these patients, and it was very difficult to distinguish between those who had received orfenso and those who had received atropine and pethidine. Particularly surprising was the hardly noticeable tachycardia in the atropine group, and a careful study of the cards yielded nothing significant to distinguish the two groups from each other. No premedication at all was given to 5 consecutive patients. In all 5 difficulty was encountered in rendering them anaesthetic during the time between the injection of methohexitone and the administration of halothane vapour; the stormy inductions were accompanied by increase in the systolic blood pressure and all kinds of active muscular movements. It is our intention to use this technique of drug-evaluation in a far greater number of cases, with improved control and documentation.

At Edenvale Hospital the drug orfenso was given to patients who complained of severe pain, and who required only a minor manipulation or incision; the procedure was usually accomplished, after orfenso had been given, without any further analgesic or anaesthetic drug. Thus, in 20 consecutive cases the results were carefully recorded on the protocols in Table I, and were found to be indistinguishable from those which follow the administration of morphine. In fact they were perhaps even better, because there was a marked absence of somnolence and other side-effects common enough after an opiate. Orfenso-compound has been used constantly for many months in the surgical wards at Edenvale Hospital with excellent results. The tablets were used predominantly in adult patients, whereas the suppositories were found very useful and practicable in infants and older children.

DISCUSSION

In the management of pain, drugs give relief in two ways: firstly by reducing the ability of the patient to perceive the sensation of pain, probably by an action on the thalamus, and secondly by modifying the appreciation of the sensation so that it is no longer unpleasant, probably by an action on the cortex. It is likely that any drug which has the second property is capable of inducing addiction.[5] The ideal analgesic would be one which is perfectly effective by the first mechanism, and which has no other effects at all.[5] A devious recognition of this principle was the combination, with morphine, of analeptics such as ethyl-methyl-glutarimide (bemegride, 'megimide'). Orfenso-compound seems to us to possess these desirable characteristics of potency combined with a total lack of habituation; it also reduces the ability of the patient to per-

ceive pain directly without somnolence, tranquillization or psycholeptic effect—side-effects essentially indicative of addiction liability. Among all the innumerable presently available non-narcotic analgesics, orfenso appears to be the most worthy product for further study.

SUMMARY

Clinical trials from two hospitals, including a small double-blind study, indicate that orfenso (piperidyl-diphenyl-hexanone) is worthy of further trials as an analgesic for general use in medicine. Its potency was found to be superior to propoxyphene, and approximately the same as that of morphine. Orfenso did not give rise to vomiting or nausea, and drowsiness was not apparent after its use. It seems to be indicated in all types of severe pain; it often rendered parenteral opiates unnecessary. After small oral doses its effect was apparent within 20 minutes and lasted 6 - 8 hours.

No habituation or addiction was noted or expected in this series, which included some patients with inoperable cancer. Orfenso produced less depression of the central nervous system, and also less respiratory and cardiovascular disturbance than is usually encountered after morphine and other opiates.

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Continental Ethicals, Johannesburg, readily provided the orfenso-compound tablets and suppositories, as well as several hundred printed protocols, and Eli Lilly S.A., Geneva, also of Johannesburg, was similarly prepared to give us as much doloxene and vondar compounds of propoxyphene as we required.

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