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ANALGESIC ACTIVITY OF (+)-1-(3-METHYL-4-MORPHOLINO-2 : 2-DIPHENYLBUTYRYL)PYRROLIDINE (R.875) IN STUDENT VOLUNTEERS

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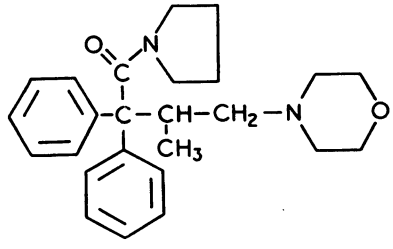
(+)-1-(3-Methyl-4-morpholino-2 : 2-diphenylbutyryl)pyrrolidine (R.875) raised the threshold to ischaemic pain in healthy human volunteers. The peak effect for all doses was reached after about 2 hr. The drug frequently caused nausea and vomiting but no euphoria. Muscular weakness was experienced by many subjects and was sometimes followed 1 to 2 hr. later by hiccup and muscle twitching, suggesting that R.875 may have an effect on striped muscle.

Between 1954 and 1956 Janssen and his co-workers synthesized and examined pharmacologically more than 600 new diphenylpropylamines. Among them was found a number of analgesics, the most potent of which was (+)-1-(3-methyl-4-morpholino - 2:2 - diphenylbutyryl)pyrrolidine. This is an optically active compound with the structural formula—



The racemic form of this compound was designated by Janssen (1956) R.610. The dextrorotatory isomer, which was found in animal experiments to be twice as active an analgesic as the racemic form, was called R.875.

In animal experiments, Janssen and Gageneau (1957), using mechanical and electrical methods of stimulation, found that R.875 was from 8 to 35 times as potent an analgesic as morphine. They also observed that the therapeutic index of R.875 was higher than that of morphine for rats and mice. Janssen (private communication) was unable to demonstrate the development of tolerance to the analgesic effect of R.875 in rats, mice or dogs.

Whilst no estimates are available of the analgesic activity of R.875 in man, a clinical trial of its isomer R.610 reported by Janssen (private communication) indicates that, weight for weight, R.610 is a more potent analgesic than morphine when pain is due to carcinoma, but less effective than morphine in controlling post-operative pain. Janssen found that vomiting rarely occurred in man even after large doses of R.610 or R.875. He reports that there was no visible respiratory depression, foetal or maternal, when subcutaneous doses of up to 40 mg. R.875 were given late in labour. The only side-effect experienced after R.875 was observed after subcutaneous injection of 10 mg. or oral administration of 20 mg. and was a curious feeling of "heaviness in the head" lasting from 15 min. to 1 hr. There was no marked euphoria in the normal subject.

It seemed advisable, as a preliminary to a clinical trial of R.875, to carry out an experiment on human volunteers to find out whether R.875 raises the pain threshold in man, to discover the nature and severity of side-effects, and to construct a dose/response curve for the drug from which doses suitable for a clinical trial could be selected.

METHODS

Selection of Subjects.—21 subjects, who had previously taken part in a similar experiment with dipipanone HCl, were asked to participate in the experiment. This method of selection was used so that a direct comparison between the effects of dipipanone HCl and R.875 on the same subjects could be made. It

also had the advantage that the subjects were already trained in the method to be used.

Doses.—These were selected to form a logarithmic series, namely 2.96, 4.44, 6.67, and 10.0 mg. A dose of 10.0 mg. was chosen as the highest because Janssen has reported that side-effects in man are only observed regularly after doses higher than this. Before beginning the investigation the author received doses of 10 mg. and 20 mg. to ensure that there would be no danger to the subjects from the doses to be used.

All doses were administered in a volume of 1.0 ml. distilled water. The ampoules containing the drug were sterilized before use by autoclaving for 20 min. at 12 to 15 lb. pressure. Distilled water, rather than saline, was used as a solvent because of lack of information regarding the solubility of R.875. As a control, 1.0 ml. distilled water was used. The subjects were unaware that an "inert" control was to be incorporated in the experiment.

Allocation of Doses.—Randomization of doses was not carried out, since this procedure was thought unsafe with a relatively unknown drug. For the same reason a double-blind technique was not employed. The doses were given to each subject in ascending order, but the control injection was given last of all.

Administration of Drugs.—All doses were administered by subcutaneous injection from ampoules which were identical in appearance. The subjects knew the drug only by its code name and were at all times unaware of the doses being used. They were not told anything about the chemical structure of the drug, but they were informed that it was believed to be an analgesic.

Procedure.—The subjects attended the laboratory in small groups on days convenient to them. The only limitation imposed upon their attendance was that at least 48 hr. were allowed to elapse between injections.

The method of estimating pain threshold has been described in detail elsewhere (Cahal, 1957). Pain was produced by ischaemic contractions of the muscles of the forearm, the venous and arterial circulations being occluded by a sphygmomanometer cuff placed around the upper arm and inflated to 220 mm. Hg. The number of ischaemic contractions necessary to produce pain was noted; the subject then continued the contractions until the pain was, in his or her estimation, moderate. The second reading was also recorded and the mean of the two readings taken as an index of pain threshold.

Following a control observation the drug was injected and observations were made at hourly intervals thereafter up to a total of 6 hr. after injection.

After injection the number of contractions necessary to produce pain increased. This increase was regarded as a measure of the rise in pain threshold following injection, and the response was recorded as the difference between the number of contractions necessary to produce pain, as described above, before and after injection.

A space was provided on the record sheet in which subjects could note side-effects.

RESULTS

Two mean observations out of a total of 735 were obtained by extrapolation because on these occasions the subjects were compelled by fatigue to stop contractions before the pain threshold was reached.

Fig. 1 shows that by 4 hr. after injection analgesia had passed its mean peak for the group. The analgesic effect of each dose was therefore

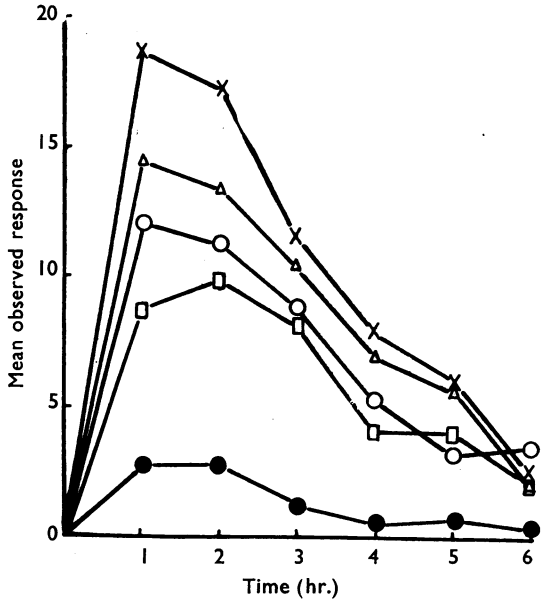


FIG. 1.—Mean observed responses of 21 subjects at hourly intervals after injection of distilled water (●), 2·96 (□), 4·44 (○), 6·67 (△) and 10·0 mg. (X) of R.875. The response is measured as the difference between the number of ischaemic contractions of the forearm muscles necessary to produce pain before and after injection.

estimated by taking the highest individual response for each subject in the first 4 hr. after injection. In this way a few isolated high responses which occurred several hours after injection were excluded.

Table I gives the results of the analysis of variance of the data obtained from the experiments, excluding the control injection, and shows that: (1) There is no evidence that the dose/response relation over the range of doses used is other than linear, (2) there is a significant difference in response both between subjects and between doses, and (3) increasing the dose of R.875 increases the ability of the drug to raise the pain threshold.

TABLE I

ANALYSIS OF VARIANCE OF THE RESULTS OF EXPERIMENTS TO SHOW THE ABILITY OF R.875 TO RAISE THE THRESHOLD TO ISCHAEMIC PAIN IN 21 HUMAN VOLUNTEERS

	Sum of Squares	Degrees of Freedom	Mean Square	Variance Ratio	P
Regression ..	1,015·26	1	1,015·26	12·85	< 0·001
Linearity ..	279·73	2	139·86	1·77	0·1–0·2
Doses	1,294·99	3	431·66	5·47	0·001–0·01
Subjects ..	3,780·24	20	189·01	2·39	0·01
Error	4,501·76	57	78·98	—	—
Total ..	9,576·99	83	—	—	—

Fig. 2 shows the calculated regression line and the mean observed responses to each dose for the whole group of 21 subjects. The equation expressing the relation between dose and response for this group is also given in Fig. 2.

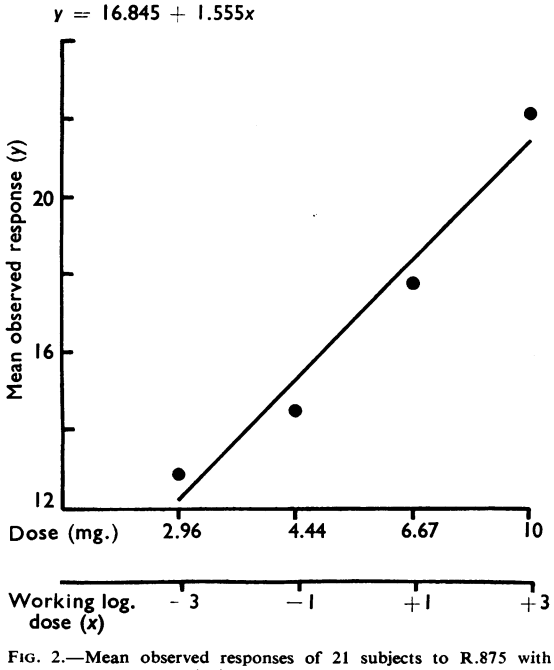


FIG. 2.—Mean observed responses of 21 subjects to R.875 with calculated regression line.

Of the 21 subjects taking part in this experiment, two had been unable to complete a similar experiment with dipipanone hydrochloride because they were hypersensitive to the drug (Cahal, 1957). Therefore, in comparing the effects of R.875 and dipipanone hydrochloride, the results obtained by these two subjects have been excluded.

Table II gives the results of the analysis of variance of the data obtained from the remaining 19 subjects on R.875, and Table III gives the results for the same group on dipipanone hydrochloride. The calculated regression lines with mean observed responses for this group on both dipipanone hydrochloride and R.875 are shown in Fig. 3, which also shows the mean observed responses to the "inert" control injections in both series of experiments.

TABLE II

ANALYSIS OF VARIANCE OF THE RESULTS OF EXPERIMENTS TO SHOW THE ABILITY OF R.875 TO RAISE THE THRESHOLD TO ISCHAEMIC PAIN IN 19 HUMAN VOLUNTEERS

	Sum of Squares	Degrees of Freedom	Mean Square	Variance Ratio	P
Regression ..	1,441·05	1	1,441·05	19·24	< 0·001
Linearity ..	660·80	2	330·40	4·41	0·1–0·2
Doses ..	880·25	3	293·42	3·91	0·001–0·01
Subjects ..	3,457·00	18	192·06	2·56	0·001–0·01
Error ..	3,819·00	51	74·88	—	—
Total ..	8,156·25	75	—	—	—

TABLE III

ANALYSIS OF VARIANCE OF THE RESULTS OF EXPERIMENTS TO SHOW THE ABILITY OF DIPIPANONE HYDROCHLORIDE TO RAISE THE THRESHOLD TO ISCHAEMIC PAIN IN THE 19 VOLUNTEERS WHOSE RESULTS ARE ANALYSED IN TABLE II

	Sum of Squares	Degrees of Freedom	Mean Square	Variance Ratio	P
Regression ..	3,823·33	1	3,823·33	48·90	< 0·001
Linearity ..	294·92	4	73·73	—	—
Doses ..	4,118·25	5	823·65	10·53	< 0·001
Subjects ..	4,383·12	18	243·51	3·11	< 0·001
Error ..	6,646·25	85	78·19	—	—
Total ..	15,147·62	113	—	—	—

Table IV shows the incidence of side-effects in the group of 21 subjects after distilled water and the four doses of R.875 which were used in these experiments.

DISCUSSION

Fig. 3 shows a striking difference between the mean observed responses to the "inert" control in the experiments on dipipanone hydrochloride and those in the experiments on R.875. The reason is probably that, despite the ignorance of the subjects of the nature of the injection given at any time, the side-effects of R.875 were so marked and so rapid in onset that their absence after an injection of distilled water made it obvious to the subjects that they had had either a very low dose of the drug or an "inert" control injection. This

difference between responses to control injections makes it pointless to attempt any accurate statistical comparison of the pain-threshold-raising capabilities of R.875 and dipipanone hydrochloride. Better experimental design would have overcome this to some extent, because, even though randomization of the doses of R.875 was not considered safe, there was really no reason why, say, half the group should not have had the control injection at the beginning of the series and half at the end. In this way the results of " expectation of side-effects " might have been diminished.

Side-effects of R.875 were very marked even on the lowest dose. They appeared within 5 min. of injection, but rarely lasted for more than an hour. The incidence of nausea even on the lowest dose was almost 50%, and after 10.0 mg. 33.3% of the subjects vomited. It is thus clear from Fig. 3 that, in healthy human subjects, R.875 cannot raise the threshold to ischaemic pain as much as can dipipanone hydrochloride because side-effects limit the dose which can be given. The count of minor side-effects on the higher doses of R.875 is probably inaccurate because many subjects were so distressed by nausea and vomiting that the less unpleasant effects were unnoticed.

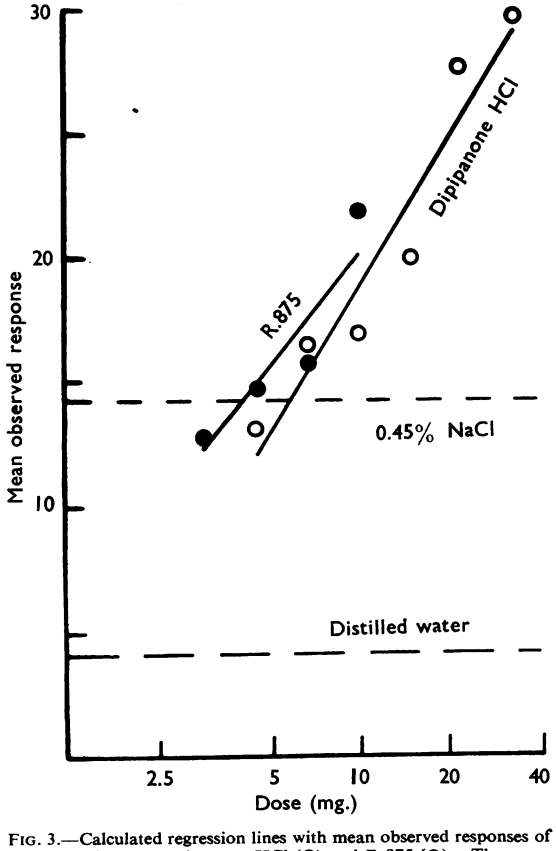


FIG. 3.—Calculated regression lines with mean observed responses of 19 subjects to dipipanone HCl (O) and R.875 (●). The mean observed responses to 0·45% saline and distilled water, which were used as controls in the experiments with dipipanone HCl and R.875, respectivelv, are shown as broken lines.

TABLE IV

INCIDENCE OF SIDE-EFFECTS AFTER INJECTIONS OF DISTILLED WATER AND VARIOUS DOSES OF R.875

Side-effect	Dose (mg.)					
	Distilled Water	2·96	4·44	6·67	10·0	Totals
Nausea	2	10	10	9	16	47
Vomiting	0	1	3	6	7	17
Dizziness	0	7	10	12	12	41
Drowsiness	1	7	7	10	11	36
Nystagmus	0	4	7	7	12	30
Pruritus	1	3	3	5	9	21
Muscular weakness	0	1	4	5	9	19
Ataxia	0	2	5	4	7	18
Visual disturbance	0	5	3	3	6	17
Headache	2	3	4	5	2	16
Flushing	0	2	2	4	5	13
Dry mouth	0	3	2	3	3	11
Inability to concentrate	0	2	3	1	4	10
Sweating	0	2	2	2	3	9
Shivering	0	0	1	1	4	6
Muzziness	0	3	2	1	0	6
Pallor	0	1	2	2	1	6
Muscle twitches	0	0	0	0	5	5
Hiccup	0	1	0	1	2	4
Sleep	0	0	2	0	2	4
Dissociation	0	1	1	0	1	3
Deafness	0	1	1	0	1	3
Eructation	0	0	0	0	2	2
Inability to swallow	0	0	0	1	1	1
Totals	6	59	74	82	125	346

An interesting observation is the absence of euphoria after the drug. This is most unusual in an analgesic of this potency, and supports the view of Janssen that R.875 produces analgesia without psychical effects.

On 19 occasions volunteers experienced marked muscular weakness, occurring about 30 min. after injection and lasting about half an hour. The frequency of this observation increased with increasing dosage and prompted the suggestion that the drug might have a paralysing effect on striped muscle. Preliminary experiments with the isolated rat diaphragm appear to confirm this, but further work will be necessary before definite conclusions can be reached.

A further indication that R.875 may have an effect on striped muscle is the occurrence of hiccup and muscle twitches. These effects appeared 2 to 3 hr. after injection and may be associated with recovery from paresis of striped muscle.

In conclusion it may be said that R.875 is a potent analgesic. Inspection of the regression lines calculated for the same group of subjects shows that its ability to raise the threshold to ischaemic pain in healthy volunteers is, weight for weight,

equal to or slightly greater than that of dipipanone hydrochloride. The dose which can be given therapeutically is limited by the severity of the side-effects and should probably not exceed 6.0 mg. by subcutaneous injection.

I am indebted to Dr. F. Prescott, of the Wellcome Foundation, for supplies of R.875, to Dr. Paul Janssen for access to his work before its publication, and to the students of the Leeds School of Medicine for their enthusiastic co-operation.

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