*Brit. J. Pharmacol.* (1957), **12**, 97.

# ANALGESIC ACTIVITY OF DIPIPANONE HYDROCHLORIDE IN STUDENT VOLUNTEERS

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(RECEIVED OCTOBER 18, 1956)

Dipipanone hydrochloride raised the threshold to ischaemic pain in healthy human volunteers. The lowest dose producing a significant rise in pain threshold was 10.0 mg. The peak effect for all doses was reached after about 2 hr. Side effects, the most common of which were drowsiness, nausea, and vertigo, are described and analysed. The drug was shown to be a histamine liberator and to cause pain and tenderness at injection sites.

During a clinical trial of dipipanone hydrochloride as an analgesic, it appeared that the doses used, 25.0 and 37.5 mg., might be at the top of the dose-response curve. It was, therefore, decided to try to construct a dose-response curve for the drug, using healthy human volunteers.

## METHODS

*Selection of Subjects.*—The proposed experiment was explained to fourth-year medical students, and volunteers were asked to write their names on a sheet of paper passed round the class. No reward was promised. Twenty-three students offered to take part in the experiment, and three more subjects were obtained from the staff of this department.

*Doses.*—These were selected to form a logarithmic series which would, in the light of experience gained from the clinical trial, be likely to give at least two doses at the top of the dose-response curve. The doses selected were 4.4, 6.7, 10.0, 15.0, 22.5, and 33.75 mg. Since it was known that the drug was painful when given by subcutaneous injection, 0.5 N-saline was used as a control rather than normal saline. The subjects were unaware that an "inert" control was being used.

*Allocation of Doses.*—Each dose was randomly allotted a code letter, and the names of the subjects were written down in random order. The dose each subject was to receive on a given day of the experiment was allotted according to the elements of a completely randomized Latin square.

*Administration of Drugs.*—All doses were administered by subcutaneous injection in a volume of 1.0 ml. The ampoules were identical in appearance, and the volunteers were unaware of the dose given or of the code letters allocated to the doses.

*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 analgesic activity of the drug was assessed by a method based upon that described by Keele (1952). Each subject was provided with a sphygmomanometer and a spare sphygmomanometer bulb. The cuff was placed around the upper arm—the right arm if the subject was right-handed, the left if left-handed—and inflated to a pressure of 220 mm. of mercury to occlude both venous and arterial circulations. In time to a neon timer which gave an audible pulse every second the subject squeezed the spare bulb with the hand to which the circulation was occluded. The number of squeezes necessary to produce pain in the forearm was noted; the subject then continued squeezing until the pain was, in his or her estimation, moderate. This second reading was also recorded, and the mean of these two readings was taken as an index of pain threshold.

Following a control observation, the drug was injected and further readings were taken at 10-min. intervals during the first hour, and at hourly intervals thereafter, up to a total of 8 hr. after the injection. One full series of observations was made before starting the experiments in order to give the subjects experience in the method.

After injection of the drug, and, to a less extent, after the injection of saline, the number of contractions necessary to produce pain increased. This increase was taken as a measure of the rise in pain threshold following injection, and was called the response. No metameter was used, the response being simply recorded as the difference between the number of contractions necessary to produce pain, as described above, before and after injection.

Each subject used the same spare bulb throughout each day's work, and care was taken to ensure that the bulb was held in the same position in the hand for all observations.

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

## Results

Of twenty-six subjects, two were hypersensitive to the drug ; their results have been excluded since it was impossible to assess them. One was unable to reach pain threshold after any dose above 6.7 mg. and experienced generalized pruritus on all doses, with severe nausea and vomiting on the two highest doses. The other became very euphoric and garrulous even on the lowest dose. The two highest doses caused severe nausea and vomiting, and on the highest dose he was disorientated, ataxic and so prostrate with vomiting that he was unable to carry out the experiment after the first 20 min.

The exclusion of these two subjects meant that the Latin square design of the experiment broke down and could not be reconstructed. It has not, therefore, been possible to obtain any information on tolerance either to the drug or to the experimental method.

Nine mean observations out of a total of 2,352 have had to be obtained by extrapolation because, at the times in question, the subjects involved were unable to reach pain threshold. These nine observations were distributed among three subjects as shown in Table I.

Table II shows that by 4 hr. after injection analgesia had passed its mean peak for the group. The analgesic effect of each dose was therefore estimated by taking the highest individual response for each subject in the first 4 hr. after injection. Thus a very few freak readings occurring several hours after injection were excluded.

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

The equation expressing the relationship between dose and response is given in Fig. 1, which

TABLE I

DISTRIBUTION OF NINE OCCASIONS ON WHICH SUBJECTS WERE UNABLE TO REACH PAIN THRESHOLD AFTER SUBCUTANEOUS INJECTION OF DIPIPANONE HYDROCHLORIDE

| Subject | Dose (mg.) | Observations | |
|---|---|---|---|
| | | No. | Times |
| A. S.♀ .. .. | 22·5 | 5 | 2, 3, 4, 5, 6 hr. |
| J. M. Bk. .. | 33·75 | 3 | 40, 50, 60 min. |
| J. G. D. .. .. | 33·75 | 1 | 3 hr. |

TABLE II

MEAN OBSERVED RESPONSES FOR ALL SUBJECTS UP TO 5 HR. AFTER INJECTION OF DIPIPANONE HYDROCHLORIDE

The response is the difference in the number of contractions necessary to produce pain before and after injection.

| Dose | Response at | | | | |
|---|---|---|---|---|---|
| | 1 hr. | 2 hr. | 3 hr. | 4 hr. | 5 hr. |
| 0·5 N-saline .. | 11 | 10 | 8 | 7 | 5 |
| 4·4 mg. dipipanone | 12 | 12 | 10 | 8 | 7 |
| 6·7 ,, ,, .. | 11 | 13 | 12 | 9 | 7 |
| 10·0 ,, ,, .. | 13 | 13 | 13 | 11 | 11 |
| 15·0 ,, ,, .. | 14 | 16 | 14 | 12 | 11 |
| 22·5 ,, ,, .. | 19 | 24 | 21 | 21 | 17 |
| 33·75,, ,, .. | 24 | 24 | 23 | 18 | 15 |

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 HUMAN VOLUNTEERS

| Item | SS. | d.f. | MS | VR | P |
|---|---|---|---|---|---|
| Regression .. | 4,195·84 | 1 | 4,195·84 | 40·60 | < 0·01 |
| Linearity .. | 128·20 | 4 | 32·05 | — | — |
| Doses .. | 4,324·04 | 5 | 864·81 | 8·368 | < 0·001 |
| Subjects .. | 11,436·16 | 23 | 497·22 | 4·811 | < 0·001 |
| Error .. | 11,884·13 | 115 | 103·34 | — | — |
| Total .. | 27,644·33 | 143 | — | — | — |

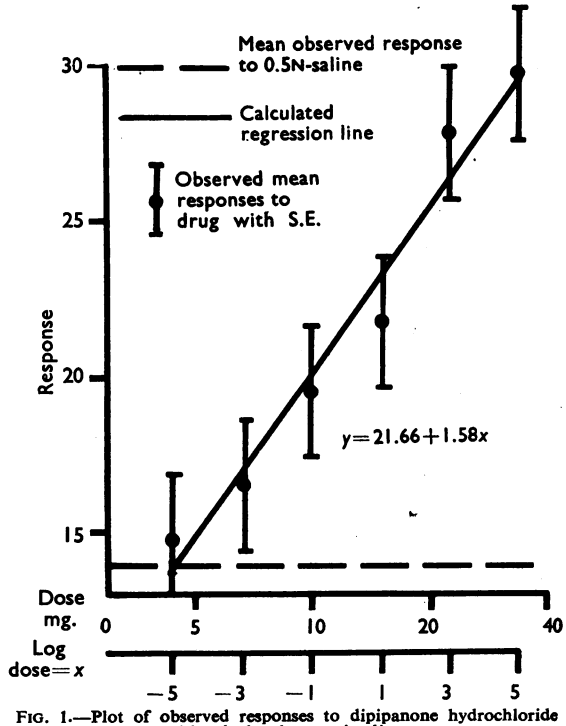


FIG. 1.—Plot of observed responses to dipipanone hydrochloride with calculated regression line.

also shows the mean observed responses to each dose with the calculated regression line.

Because there was an apparent analgesic response to 0.5N-saline, it was of interest to determine whether the variance in "response" to saline was similar to that observed with the drug. From the data obtained by experiment the variance of "responses" to 0.5N-saline is 68.78; there is no significant difference between this and the variance of response to the drug. The mean "response" to 0.5N-saline is shown in Fig. 1.

Having established this lack of significant difference in the variance of response between 0.5N-saline and the drug, the lowest dose of dipipanone hydrochloride in the series which would cause a significant rise in pain threshold was determined. As shown in Table IV, a dose of 10 mg. causes a rise in pain threshold which is barely significant.

TABLE IV

"$t$" TEST SHOWING THAT 10 MG. DIPIPANONE HYDROCHLORIDE PRODUCES A RISE IN PAIN THRESHOLD WHICH IS JUST SIGNIFICANT

Mean response to saline .. .. .. .. $=13{\cdot}79 \pm 3{\cdot}71$

Calculated response to 10 mg. dipipanone HCl .. $=20{\cdot}08 \pm 2{\cdot}12$

$$t(46) = \frac{20{\cdot}08 - 13{\cdot}79}{\sqrt{\frac{68{\cdot}78}{23} + \frac{103{\cdot}34}{23}}} = 2{\cdot}298$$

$P = 0{\cdot}02\text{–}0{\cdot}05$

*Side Effects.*—The incidence of side effects is shown in Table V. Not all of these effects can be regarded as undesirable. Drowsiness, euphoria, sleep, and "detachment," for instance, are effects which enhance the value of a major analgesic.

TABLE V

INCIDENCE OF SIDE EFFECTS AFTER INJECTIONS OF 0·5 N-SALINE AND VARIOUS DOSES OF DIPIPANONE HYDROCHLORIDE

| Side Effects | Dose (mg.) | | | | | | | Total |
|---|---|---|---|---|---|---|---|---|
| | Saline | 4·4 | 6·7 | 10·0 | 15·0 | 22·5 | 33·75 | |
| Drowsiness .. | 1 | 3 | 2 | 7 | 8 | 14 | 16 | 51 |
| Nausea .. .. | 2 | 3 | 2 | 5 | 5 | 14 | 17 | 48 |
| Dizziness .. | 0 | 0 | 2 | 4 | 5 | 10 | 18 | 39 |
| Euphoria .. | 0 | 2 | 0 | 4 | 5 | 4 | 10 | 25 |
| Muzziness .. | 0 | 0 | 0 | 2 | 3 | 6 | 6 | 17 |
| Vomiting .. | 0 | 0 | 0 | 0 | 0 | 2 | 8 | 10 |
| Headache .. | 1 | 2 | 3 | 2 | 3 | 5 | 4 | 20 |
| Dry mouth .. | 0 | 0 | 2 | 0 | 1 | 5 | 6 | 14 |
| Ataxia .. .. | 0 | 0 | 1 | 0 | 1 | 5 | 6 | 13 |
| Epigastric discomfort .. .. | 0 | 1 | 1 | 3 | 2 | 0 | 1 | 8 |
| Detachment .. | 0 | 0 | 0 | 1 | 1 | 2 | 4 | 8 |
| Pruritus .. | 0 | 1 | 0 | 0 | 2 | 1 | 4 | 8 |
| Tremors .. | 0 | 0 | 0 | 0 | 0 | 2 | 5 | 7 |
| "Constriction" of the throat.. | 0 | 0 | 0 | 1 | 1 | 1 | 4 | 7 |
| Anorexia .. | 0 | 0 | 0 | 0 | 0 | 3 | 1 | 4 |
| Irritability .. | 0 | 0 | 0 | 0 | 0 | 1 | 1 | 2 |
| Deafness .. | 0 | 0 | 0 | 0 | 0 | 1 | 1 | 2 |
| Sleep .. .. | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 1 |
| Total .. | 4 | 12 | 13 | 29 | 37 | 76 | 113 | 284 |

Table V shows that there is a sharp rise in side effects when the dose exceeds 15 mg. and it is felt that this imposes a limit on the dose which should be used therapeutically.

It should, however, be stressed that the subjects were healthy volunteers and that the incidence of side effects—particularly dizziness, nausea and vomiting—might be expected to be greater in such subjects than in the patients confined to bed for whom dipipanone hydrochloride would be most likely to be used. Indeed, it was noteworthy that many subjects found that on lying down these symptoms were absent or not so marked. Two subjects were nauseated in the laboratory, but only vomited when going home by bus. Therefore, although the optimum dose in subjects who were up and about was about 20 mg., in recumbent patients it might justifiably be increased to 25 mg.

The generalized pruritus of which some subjects complained was rather distressing and persisted for many hours. This effect, together with the incidence of headache and epigastric discomfort, prompted the suggestion that dipipanone might be a histamine-liberator. Intradermal injection of dipipanone hydrochloride did produce a weal and flare reaction, and the area of the weal was decreased by the previous administration of 2.5 mg. triprolidine hydrochloride by mouth.

All the injections were painful and often the pain was very persistent. Many subjects had tenderness and induration at the sites of subcutaneous injection for many weeks. Slight ulceration occurred at the sites of intradermal injections. The ulcers were slow to heal and have left pigmented scars.

The inability of some subjects to reach pain threshold on occasion was probably due in part to the hypnotic effect of the drug and not solely to its analgesic action. For instance, 50 min. after a dose of 33.75 mg. one subject was compelled by fatigue to stop squeezing the bulb after 75 squeezes although no pain had been felt. After 180 min., however, he was able to squeeze the bulb 90 times and reach pain threshold.

My thanks are due to Dr. J. G. Dare for his invaluable assistance with the analysis of the results, to Professor W. A. Bain and my colleagues for their interest and encouragement, and not least to the volunteers for their willing and cheerful co-operation. I am indebted to the Wellcome Foundation for supplies of dipipanone hydrochloride.

REFERENCE

Keele, C. A. (1952). *Analyst*, 77, 111.