# Analgesic Properties of Xylopropamine.* (23170)

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Information that sympathomimetic drugs are analgesic has been accumulating for more than 50 years. Thirteen earlier reports (beginning in 1904) of clinical and laboratory experiences were cited by Ivy, *et al.*(1), when they confirmed Weber's(2) observation that epinephrine given intracarotidly conferred profound analgesia without alteration of other conscious behavior. Ivy used dogs. Weber used cats. Epinephrine, ephedrine, and amphetamine were employed in the several studies referred to. More recently, additional evidence has accrued. Leimdorfer(3) produced profound clinical analgesia by intraspinal administration of epinephrine. Amphetamine potentiation of morphine analgesia has been reported by Goetzl and Burrill in animals(4) and man(5). That amphetamine alone can elevate the pain threshold has been reported by Burrill, Goetzl, and Ivy(6) and by Harris and Worley(7). Physiologically occurring epinephrine may participate in the production of analgesia by certain established compounds (like morphine). Friend and Harris(8) and Gross, *et al.*(9), found ablation of adrenal medullae to reduce the analgesic potency of said compounds. Exactly what "analgesia" may be remains a mystery. That the pain experience is a complex and variable combination of perception and interpretation seems to be a general observation acceptable to most algesimetricians and clinicians. This is reflected in their reports that some "analgesics" do not reduce the pain sensation but make it more tolerable to the patient or render him indifferent to the pain, *i.e.*, patient "suffering" is reduced while the perceptual experience persists. Such a mechanism of "analgesia" has been attributed frequently to the opiates and to the sympathomimetics. Evidently, indifference to pain is thought to be favored by narcosis and/or analepsis—an easily enough formulated hypothesis but one not particularly tenable. Analgesia with narcotics is enhanced by the addition of analeptic sympathomimetics(5) and the addition of barbiturates to sympathomimetic analeptic analgesics does not diminish their analgesic effectiveness(7). An amphetamine compound which is analgesic but not stimulating might further disassociate analepsis from analgesia, as well as providing certain clinical conveniences. According to reports from the manufacturers' laboratories, xylopropamine sulfate† (1-(3,4-Dimethylphenyl)-2-Aminopropane) is one-third to one-fifth as stimulating as dextro-amphetamine. Thus, evaluation of its analgesic properties seemed appropriate.

*Method.* Each of 8 male human volunteers served for 4 experiments, in which the threshold to experimentally induced pain was determined at intervals before and after oral medication according to the method of Harris and Blockus(10). *Medications* were: A. placebo, B. 5 mg xylopropamine sulfate, C. a "dry-run" in which no capsule was taken, and D. 10 mg xylopropamine sulfate. All capsules were prepared to look alike and were taken with water at least 4 hours postprandial. *Medication sequence* was according to a "latin-square" design so that each treatment was the first for 2 subjects, second for 2 subjects, etc. *Stimuli* were square waves of one millisecond duration automatically generated every 0.5 second. Intensity of the stimulus was slowly increased in one millivolt steps until the subject signaled that he felt pain. The process was then immediately repeated. Both values, so obtained, were recorded. The *stimulus sites* were metal restorations in vital teeth. Only "Class I" fillings (in the occlusal plane with no overlap beyond the crown of the tooth) were used. The same site was always used in each man's mouth. Before placing the electrode against the "filling," the surface was carefully dried with ethyl alcohol, cotton rolls being inserted on

* Aided in part by grant from Hoffmann-La Roche.

† Supplied by Hoffmann-LaRoche, Inc.

TABLE I. Average Increments in Millivolts of Pain Thresholds after Placebo, "Dry-run", 5 mg and 10 mg Oral Doses of Xylopropamine.

| Min. after medication | Placebo | "Dry-run" | Xylopropamine 5 mg | Xylopropamine 10 mg |
|---|---|---|---|---|
| 30 | 15.6 | -142.0 | - 68.5 | -72.5 |
| 60 | -314.4 | - 75.0 | -192.5 | 109.4 |
| 90 | -269.1 | -292.5 | -214.4 | 105.6 |
| 120 | 3.8 | -367.5 | - 43.1 | 168.1 |
| 150 | -206.2 | -416.2 | - 11.9 | 565.0 |
| 180 | -267.0 | -395.0 | .6 | 437.0 |

the labial border of the site. It is imperative that the surface of the tooth be dry to prevent dissipation of current around the pulp rather than through it. The indifferent electrode from the stimulator is placed in a beaker of saline solution with one of the subject's hands. *Intervals* were 30, 15 and 1 minutes prior to ingestion of drugs and 30, 60, 90, 120, 150, and 180 minutes after. The interval between experimental sessions was never less than 48 hours. Bias was controlled by "triple blind" discipline. Except for the "dry-run," neither operator nor subjects knew medication identities until the entire study was completed. Which subject was which was unknown to the director of the study. This control was achieved by labeling in advance 4 small envelopes for each subject with his number in a Roman numeral (Subject I) and the experiment number in an Arabic (Exp. 1). These 32 envelopes were filled according to the protocol and stapled shut. This process was checked 3 times for accuracy. To confirm proper chronology of treatment, when an envelope was opened by a subject, it was returned to the operator who stamped the date on it. To be assured against the need for emergency identification of a medicament, it is standard practice in this laboratory to provide the operator with an opaque, sealed envelope containing the code. Appropriate antidotes or other emergency materials are always immediately available.

*Results.* The average value of each individual dial reading in the raw data was converted to millivolts from the calibration curve of the stimulator and recorded on a master table for each medication. These data, in turn, were simplified further by recording the post-medication increments from the average of the second and third premedication thresholds, and then recorded in Table I as average increments in millivolts per treatment and interval.

Whether or not the differences evident in Table I are real cannot be determined with confidence by inspection. Accordingly, the increment data from which Table I was derived were subjected to analyses of variance.

In Table II is the summary of such an analysis on the entire data. Though there is no significant difference between the increments following dry-run, placebo and a 5 mg dose of xylopropamine sulfate, the increments following these 3 treatments are significantly inferior ($P<0.05$) to the increments following 10 mg doses of xylopropamine sulfate. It is to be pointed out that such an analysis actually compares the *average* increments throughout the entire postmedication period, even though it is quite evident that no effects really appear until more than one hour after medication.

To make the analysis more sensitive, an analysis of variance was performed on the same data by observation intervals. From the results of these analyses (Table III) it may be seen that the same conclusions as above pertain to the 150 and 180 minute postmedication intervals. A moot question thus far in algesimetry is whether to express threshold changes as absolute increments or as percent of premedication thresholds. Therefore, these data have been reevaluated

TABLE II. Summary of Analysis of Variance.

| Source | Degrees freedom | Mean square | "F" ratio |
|---|---|---|---|
| *Major* | | | |
| Subjects | 7 | 1053029 | 1.142 |
| Treatments | 3 | 2215786 | 2.403 |
| (ABC) | ( 2) | ( 898753) | .974 |
| (ABC)(D) | ( 1) | (5748606) | 6.233* |
| Subj. × treat. | 21 | 922266 | |
| *Minor* | | | |
| Times | 5 | 90899 | |
| " × subj. | 35 | 120099 | |
| " × treats. | 15 | 251941 | |
| S × T × T | 105 | 221390 | |

* $P < .05$.

TABLE III. Summary of Analyses of Variance by Postmedication Intervals.

| Interval (min.) | Source | Degrees freedom | Mean square | "F" ratio |
|---|---|---|---|---|
| 30 | Subjects | 7 | 84541 | 1.683 |
| | Treatments | 3 | 33244 | .661 |
| | S × T | 21 | 50221 | |
| 60 | Subjects | 7 | 322723 | .829 |
| | Treatments | 3 | 260431 | .670 |
| | (ABC) | ( 2) | (229227) | .580 |
| | (ABC)(D) | ( 1) | (552066) | 1.419 |
| | S × T | 21 | 389040 | |
| 90 | Subjects | 7 | 464094 | 1.607 |
| | Treatments | 3 | 273992 | .949 |
| | (ABC) | ( 2) | ( 25726) | .089 |
| | (ABC)(D) | ( 1) | (796251) | 2.757 |
| | S × T | 21 | 288768 | |
| 120 | Subjects | 7 | 258511 | 1.801 |
| | Treatments | 3 | 402522 | 2.804 |
| | (ABC) | ( 2) | (326991) | 2.278 |
| | (ABC)(D) | ( 1) | (553584) | 3.855 |
| | S × T | 21 | 143566 | |
| 150 | Subjects | 7 | 382393 | .595 |
| | Treatments | 3 | 1395032 | 2.107 |
| | (ABC) | ( 2) | ( 327201) | .509 |
| | (ABC)(D) | ( 1) | (3530693) | 5.490* |
| | S × T | 21 | 643164 | |
| 180 | Subjects | 7 | 145170 | .283 |
| | Treatments | 3 | 1081390 | 2.107 |
| | (ABC) | ( 2) | ( 325988) | .635 |
| | (ABC)(D) | ( 1) | (2592194) | 5.051* |
| | S × T | 21 | 513157 | |

* $P < .05$.

as percentile changes.

New tables (not appended) were prepared so that each original data cell was an expression of the increment as a percent of the premedication threshold. The results of this procedure are presented in Table IV, which is of somewhat different character than Table I with respect to the effects of "dry-run," placebo and 5 mg of xylopropamine.

The same statistical procedures as above

TABLE IV. Average Increments in Percent of Pain Thresholds after Placebo, "Dry-run", 5 mg and 10 mg Oral Doses of Xylopropamine.

| Min. after medication | Placebo | "Dry-run" | Xylopropamine 5 mg | Xylopropamine 10 mg |
|---|---|---|---|---|
| 30 | 2.26 | −1.51 | − .08 | .28 |
| 60 | −1.34 | .43 | −1.31 | 4.47 |
| 90 | − .87 | −3.82 | − .14 | 10.07 |
| 120 | 4.91 | −6.66 | 6.14 | 9.16 |
| 150 | 3.69 | −6.54 | 6.05 | 19.91 |
| 180 | .80 | −7.32 | 4.47 | 14.88 |

TABLE V. Summary of Analysis of Variance on % Values.

| Source | Degrees freedom | Mean square | "F" ratio |
|---|---|---|---|
| *Major* | | | |
| Subjects | 7 | 625.2650 | 1.052 |
| Treatments | 3 | 1591.1029 | 2.678 |
| (ABC) | ( 2) | ( 642.8832) | 1.082 |
| (ABC)(D) | ( 1) | (3487.5422) | 5.869* |
| (AB) | ( 1) | ( 21.5177) | .036 |
| (C)(AB)(D) | ( 2) | (2375.8955) | 3.998* |
| Subj. × treat. | 21 | 594.2438 | |
| *Minor* | | | |
| Intervals | 5 | 142.4264 | |
| Subj. × int. | 35 | 109.5959 | |
| Treats. × int. | 15 | 158.6389 | |
| S × T × I | 105 | 110.9249 | |

* $P < .05$.

were applied to these data and appear summarized in Tables V and VI. Again, the average effect of 10 mg of xylopropamine was superior ($P<0.05$) to the average effects of the other 3 treatments. When broken down by intervals, this relationship first appeared at 90 min. postmedication and persisted through to the final reading.

A different partitioning of treatment variance was suggested by Table IV. In this treatment, effects of A and B (Placebo and 5 mg xylopropamine) were compared and found to be similar at all intervals. However, there were statistically significant differences between treatments C (dry-run), A and B together and D (10 mg xylopropamine) 90 and 120 minutes after medication. At 150 and 180 minutes, the probability of coincidence causing the differences observed has risen to an estimated 0.07.

*Discussion.* The findings of this study strongly indicate that xylopropamine, in 10 mg oral dosage, is analgesic. The latency of response is reminiscent of experience obtained with another sympathomimetic—Daprisal(7). A possible explanation of this delay in effect, is that by its local vasoconstricting effect, the sympathomimetic delays its own absorption. Efforts to prove or disprove this hypothesis have not been made. The present evidence demonstrates a similarity of analgetic activity between xylopropamine and amphetamine. If the disparity between their

TABLE VI. Summary of Analyses of Variance by Postmedication Intervals on % Values.

| Interval (min.) | Source | Degrees freedom | Mean square | "F" ratio |
|---|---|---|---|---|
| 30 | Subjects | 7 | 20.8341 | .464 |
| | Treatments | 3 | 19.3750 | .432 |
| | S × T | 21 | 44.8773 | |
| 60 | Subjects | 7 | 260.1349 | 2.019 |
| | Treatments | 3 | 59.7446 | .464 |
| | S × T | 21 | 128.8230 | |
| 90 | Subjects | 7 | 187.1359 | 2.144 |
| | Treatments | 3 | 293.1162 | 3.358* |
| | (ABC) | ( 2) | ( 30.3779) | .348 |
| | (ABC)(D) | ( 1) | (818.5928) | 9.379† |
| | (AB) | ( 1) | ( 2.1025) | .024 |
| | (C)(AB)(D) | ( 2) | (438.6231) | 5.026* |
| | S × T | 21 | 87.2780 | |
| 120 | Subjects | 7 | 228.0122 | 2.389 |
| | Treatments | 3 | 506.7374 | 5.309* |
| | (ABC) | ( 2) | (398.6667) | 4.176* |
| | (D)(ABC) | ( 1) | (722.8788) | 7.573* |
| | (AB) | ( 1) | ( 6.0393) | .063 |
| | (C)(AB)(D) | ( 2) | (757.0864) | 7.932† |
| | S × T | 21 | 95.4441 | |
| 150 | Subjects | 7 | 323.0345 | .686 |
| | Treatments | 3 | 949.1065 | 2.018 |
| | (ABC) | ( 2) | ( 358.2576) | .762 |
| | (D)(ABC) | ( 1) | (2130.8041) | 4.532* |
| | (AB) | ( 1) | ( 22.2548) | .047 |
| | (C)(AB)(D) | ( 2) | (1412.5323) | 3.004 |
| | S × T | 21 | 470.2159 | |
| 180 | Subjects | 7 | 154.0929 | .506 |
| | Treatments | 3 | 678.6871 | 2.227 |
| | (ABC) | ( 2) | ( 291.1062) | .955 |
| | (D)(ABC) | ( 1) | (1453.8489) | 4.771* |
| | (AB) | ( 1) | ( 54.1328) | .178 |
| | (C)(AB)(D) | ( 2) | ( 990.9642) | 3.252 |
| | S × T | 21 | 304.7322 | |

* $P < .05$. † $P < .01$.

analeptic effects can be extended to include human quantitative evidence, interesting new hypotheses on the mechanism of analgesia may be formulated: *e.g.*, that sympathomimetic drugs in some way diminish the intensity of pain sensations reaching the level of perception.

*Summary.* 1) A new sympathomimetic drug, xylopropamine sulfate (1-(3,4-Dimethylphenyl)-2-Aminopropane), has been found capable of elevating the threshold of human subjects to experimentally induced pain. The method employed was electrical stimulation of the tooth pulp. There were 8 subjects and the experiment was conducted under "double blind" discipline. Five and 10 mg oral doses of xylopropamine were compared with a placebo and a "dry-run." The average effect of the 10 mg dose was statistically superior ($P < .05$) to the effects of the other treatments from 90-180 minutes after medication. 2) It is provocative that xylopropamine is analgesic but apparently not analeptic, while amphetamine is both. It suggests that the two effects on the sensorium could be independent.

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Received March 8, 1957. P.S.E.B.M., 1957, v95.