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A comparison of the effects of flupentixol and relaxation on laboratory pain: An experimental study

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ABSTRACT – The present experiment compared the effects of flupentixol (0.5 mg) and relaxation on acute laboratory pain induced by pressure. Results showed that flupentixol, in general, did not have an analgetic effect, but rather a negative effect. Relaxation with specific training for the pain site did have pain-relieving properties, while an "unspecific relaxation" control procedure did not result in significant pain relief. Possible explanations for the unexpected negative effect of flupentixol are discussed.

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The subjective experience of pain is a complex and difficult phenomenon to study. Two persons exposed to the same pain stimulus may perceive the pain in different ways. Yet, despite such problems, a good deal of research concerning pain and pain treatment is conducted. One of the reasons is that pain often is a primary purpose of a patient's visit with a physician. This research has followed 2 general lines, a medical line (with drugs, surgery, TNS, etc.), and a psychological line (with relaxation training, psychotherapy etc.). Very few attempts have been made to integrate these 2 approaches (1).

In the medical tradition, causes of pain are searched for and, if and when found, they can be corrected or compensated for. Pain experienced during the interim is treated primarily with drugs. A number of analgesics have been tested in this respect. According to recent findings, there is reason to believe that flupentixol has pain-relieving properties in chronic pain states (2). An advantage of flupentixol is that the extremely low doses thought to produce reductions in pain should have few if any side effects.

A second line of research is psychological. Pain is here viewed in part as a perceptual and psychological experience subject to learning. Many forms of behavioral treatment, for instance, have been shown to be of some promise in the treatment of chronic pain (3, 4). For acute pain, behavioral methods, e.g. coping strategies, have also been tried (5). Moreover, it has been possible to show changes in pain intensity ratings using psychological methods during a single session with experimental pain (6). A commonly used method is relaxation which, by itself and in coping programs, is believed to be of considerable help in reducing and controlling pain (3, 4, 7). One question concerning relaxation is whether an instruction which provides training specifically to the site of pain is better than a general relaxation instruction. Ordinarily, general instructions are used but specific instructions would seem to be a logical improvement.

The present experiment was conducted to test and compare the pain-relieving properties of flupentixol and relaxation. 4 groups of subjects participated in a 2 × 2 factorial design where medication (flupentixol or placebo) and relaxation (specific or non-specific) were the active treatment components.

The maximum possible attempt was made to minimize external stimuli, as these have been shown to influence pain perception (6).

Methods

Subjects

28 healthy volunteers of both sexes recruited from among medical students and employees at a psychiatric hospital participated in the experiment. No incentives were given for participation.

Design

The design used was a 2 × 2 factorial design, where the subjects were randomly assigned to one of the 4 groups consisting of 7 persons in each; 1) specific relaxation and flupentixol, 2) specific relaxation and placebo, 3) non-specific relaxation (control) and flupentixol, and 4) non-specific relaxation (control) and placebo. Flupentixol and placebo were given double-blind.

Assessments

Pain. A Visual Analog Scale (VAS) consisting of a 100 mm line, anchored at both ends (no pain, extreme pain), was marked by the subjects to indicate their degree of pain.

Side effects. All subjects were asked an open question with regards to side effects.

Double-blind check

The subjects made an evaluation during the experiment if they were given flupentixol or placebo. This was made in order to make sure that the experiment was truly double-blind. Furthermore, the experimenter made a similar evaluation, but first when the experiments was completed and the results collected. The answers were compared with the double-blind code following the completion of the entire experiment.

General procedure

Participants were met by a male experimenter. To reduce extranous effects, information was provided via standard written text and the experimenter was instructed to hold a neutral tone. Subjects were told that the experiment was a test of an analgetic drug and that they would also receive relaxation training. They were also told that the dose given was lower than the normal therapeutic dose and that no sedative effects were expected. Informed consent was obtained.

A blood-pressure cuff produced the noxious stimulation and on the first trial it was pumped up to 300 mm Hg and held there for 10 sec. Subjects then marked their experienced pain intensity on the VAS. This procedure was repeated 5 more times with a 60 sec intertrial interval to provide a pretest.

The administration of the drug (flupentixol or placebo) took place next. Then followed a 50 min waiting period during which the participants could work or read. At the conclusion of this period, they listened to taped relaxation instructions.

The non-specific relaxation procedure for Groups 1 and 3

A male experimenter gave the subjects a general non-specific relaxation instruction suggesting that the subjects sit comfortably in their chairs, close their eyes and relax. The subjects were told to think of and imagine a pleasant experience they have had; for instance, a lovely summer day. At the same time, they were instructed to concentrate on body sensations associated with relaxation in different parts of the body (right hand, wrist, lower arm, elbow, upper arm). The trainer continued: "...the whole arm is now relaxed. Do the same with your left arm, and try to get it to relax just as much as your right arm. After that you should try to relax in the rest of your body...". The subjects were further in-

structed to breathe in a slow and controlled manner.

The specific relaxation procedure for Groups 2 and 4

The instructions specific to the pain site were the same as the above but, in addition, the trainer continued: "feel the heaviness in your whole body. You are awake and alert, but also relaxed. For every expiration, your body becomes heavier and heavier. Soon you will get the cuff again. It will be pumped up as before. Concentrate on the weight and relaxation of your right arm when the pressure increases. You can control the pain that way. Now I will put on the cuff. Remember to concentrate on maximal weight in the arm when the pressure increases. The harder the pressure becomes, the more relaxed your arm will be".

Following the relaxation training (and 50 min waiting), 3 post-test pain trials were conducted in the same manner as in the pretest.

Statistics

Analyses of variance (ANOVA) were computed on the main results, followed by *t*-tests to see the contrasts between the groups (8). The check on the double-blind procedure was tested using phi-correlations (9).

Results

A one-way ANOVA showed that there were no significant differences between the groups before treatment ($F < 1$, df = 3/24, $P < 0.05$).

Table 1
Mean subjective pain scores (mm on a 100 mm VAS) before (5 test trials) and after (3 test trials) treatment (medical/psychological) and the differences, for the 4 different groups

Group	Pre	Post	Difference
1. Flup + relax	45.1	39.2	−5.9
2. Plac + relax	48.2	29.4	−21.5
3. Flup + control	35.4	38.2	+2.8
4. Plac + control	35.0	29.6	−5.5

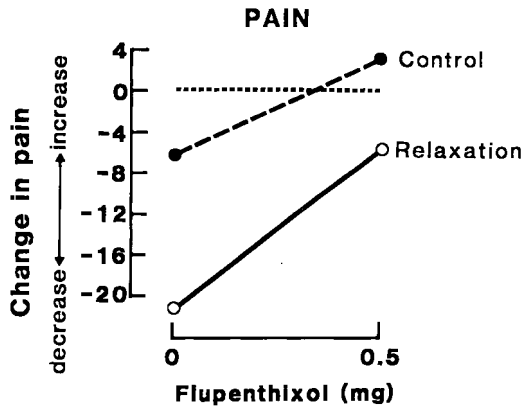

Fig. 1. The effect of flupentixol (0.5 mg/placebo) is shown for the 2 different relaxation groups (relaxation/control).

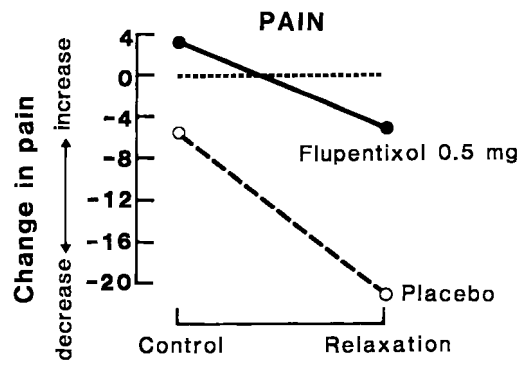

Fig. 2. The effect of relaxation (relaxation/control) is shown for the 2 drug conditions (flupentixol 0.5 mg/placebo).

Pain reduction

Changes in pain following intervention are shown in Table 1, Figs. 1 and 2. Group 2 (relaxation and placebo) was the only group with statistically significant pain reductions from pre- to post-test ($t = 2.93$, $P < 0.05$). ANOVA of the changes in the 4 groups showed significant results in the drug variable ($F = 7.43$, $df = 1/24$, $P < 0.05$) and the psychological treatment variable ($F = 6.92$, $df = 1/24$, $P < 0.05$), but no significant interaction ($P > 0.05$).

Within-group results

Group 1 (flupentixol and specific relaxation). 5 subjects felt some pain relief, while 2 felt more pain in the last part of the experiment.

Group 2 (placebo and specific relaxation). There was a significant difference between pain scores before and after treatment ($t = 2.93$, $P < 0.05$). All subjects showed a reduced pain score after the specific relaxation.

Group 3 (flupentixol and unspecific relaxation). 4 subjects felt much more pain, one felt a little bit more pain, and 2 subjects less pain in the last part.

Group 4 (placebo and unspecific relaxation). 2 felt more pain and 5 felt less pain in the last part.

Double-blind check

The subjects' own guesses were not statistically significant (phi = 0.22, $P > 0.05$).

The experimenter's estimations made after the experiment as to which drug was given were statistically significant (phi = 0.43, $P < 0.05$) but were contrary to what was expected (as flupentixol was believed to have an analgetic effect). The conclusion is that the double-blind procedure was kept blind throughout the experiment (a question which is specifically directed towards the side effects), while it was possible to reveal the code (although with wrong signs), considering the results.

Side effects

With one exception in the placebo group, no side effects were reported.

Discussion

The experiment showed that flupentixol had a harmful effect under the given circumstances, whereas a specific relaxation procedure reduced aucte pain.

Earlier research has shown that flupentixol (0.5 mg) has some analgetic effect in the treatment of chronic pain (2). The subjects in earlier studies were patients with chronic pain receiving a prolonged treatment, and flupentixol thus reached a steady-state level during treatment. In our experiment, the induced pain was acute and we never reached a steady state (one dose of 0.5 mg, 60 min). 50 min should be sufficient to give some effect, but an optimal effect might not be reached until 3 h after administration. We may also have a State Dependent Learning effect (10) which means that what you learn in a drug-induced situation or state can not easily be reproduced in another state, and vice versa.

Chronic pain is often linked to depression. This could be another reason for the effect of flupentixol in chronic pain, as it also has some degree of antidepressive effect. It is also noticed in other studies that morphine, the most potent analgesic, is effective in only about 70% of the cases in which it is used, and that it actually works through reducing anxiety, fear, worry and other emotions that are usually intermingled with pain (11, 12).

The blood-pressure cuff as a pain stimulus was not adequate, which some of the subjects also pointed out. It was not really painful, rather it produced some discomfort. We consider ice-water in a bucket to be a better pain stimulus.

Specific relaxation seems to be useful in pain relief for some subjects but not all. The reason could be that some people find it easier to relax than others. It is remarkable that so many experienced pain-relieving effects after such short relaxation training as in the present study.

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