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Role of pain in placebo analgesia

(subjective scaling/sensory modulation/visual analog scale/postoperative pain)

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ABSTRACT **The hypothesis that perceived pain intensity can influence placebo analgesia was tested. One hundred and seven subjects rated their pain from 0 to 10 on a visual analog scale after a standard wisdom tooth extraction. The expected course of such postoperative pain in the absence of therapy or placebo is a steady increase; this was confirmed by blind administration of the placebo. When placebos were given intravenously in view of the patients, some (placebo nonresponders) reported that their pain increased, whereas others (placebo responders) reported that their pain either decreased or remained the same over the next 60 min. A placebo response was more likely to occur if the pain rating 5 min prior to placebo administration (initial pain) was greater than 2.6. Furthermore, placebo responders with initial pain above this 2.6 level reported significantly greater mean analgesia than those with lower initial pain. Indeed, responders with initial pain less than 2.6 reported no change in pain during the 60 min after administration of a placebo. When their initial pain level was greater than 2.6, they reported a steady decline in pain over this period. However, above the 2.6 level there was no obvious relationship between the magnitude of the placebo analgesia and the initial pain.**

To assess the efficacy of any analgesic therapy, it must be compared to the administration of a placebo. Although placebo treatment involves administration of an inert substance, the power of the act itself to elicit analgesia is well known. Placebo shows such characteristics of a pharmacologically active drug as a dose–response curve (peak effect, cumulative action, and gradual decline) (1–3), as well as tolerance (2) and side effects (4–6). Beecher (7) has pointed out that, although over 33% of patients with various clinical pains respond to placebo with significant analgesia, only about 3% of subjects with experimental pain have an analgesic response. One explanation for this difference between experimental and clinical pain is that it is due to differences in characteristics of the pain, such as rate of rise or duration. When compared with experimental pain, clinical pain usually has a more gradual onset and a relatively long duration. Thus, these and other characteristics of the pain may be important factors in determining the efficacy of placebo analgesia. Although Lasagna *et al.* (2) noted anecdotally that patients with the most severe pain appeared less likely to respond to an analgesic placebo, we are unaware of any systematic studies on this problem.

METHODS

The details of the experimental procedure have been described (8, 9). One hundred seven patients participated in this study. Consent to act as a subject was obtained by using a form that followed the guidelines of the Committee on Human Experimentation of the University of California at San Francisco.

Subjects underwent a standardized surgical procedure for the removal of impacted mandibular third molars after premedication with 10–20 mg of diazepam. During surgery, nitrous oxide in concentrations of 15–40% and local anesthesia with 3% mepivicaine (without vasoconstrictor, having an effective duration of 45–75 min) were used. All surgeries were performed by the same oral surgeon (N.C.G.). In an adjoining recovery area, patients rated their pain by marking a 10-cm horizontal line that had the words 'no pain' at the left end and 'worst pain ever' at the right. The position of the marks, in millimeters, provided the experimental pain measure. The validity of this scale has been discussed in a previous paper (8, 9). Two hr after the onset of anesthesia, each patient was given, double-blind, a placebo or an active drug as an intravenous bolus of equal volume, and was asked to rate his or her pain 5, 20, and 60 min after administration of the placebo. Those patients receiving active drugs will not be discussed in this paper. In the discussion below, we have compared the initial pain (P) reported by the patients 5 min prior to administration of the placebo with the change in pain over the next 60 min (ΔP_{60}).

In a previous paper (9), we suggested that the normal course of pain during the 3-hr period of this study would be a progressive increase in reported severity. To test this assumption, the method of administering the saline 'placebo' was modified so that the patient was unaware that any injection had been given via their intravenous line (routinely employed in this operation), and the surgeon was unaware of what drug he had given (a blind placebo). Patients were then asked to rate their pain level at 20-min intervals throughout the 3-hr recording period, and the blind placebo was administered 2 hr after the onset of anesthesia. This procedure was carried out in eight patients. We found the mean pain of these eight patients increased steadily, before and after administration of the blind placebo. Furthermore, no patient reported a decrease in pain after receiving the blind placebo. This confirms that using this clinical paradigm, in the absence of the perceived stimuli that presumably trigger placebo analgesia, the natural course of pain is a steady increase in all patients.

RESULTS

In contrast to our earlier study (9), the greater definition afforded by the present larger sample indicated that those patients reporting an increase in pain of 0.2 or less (which is probably the margin of error of the pain estimate) should be included in the placebo responder group. Because the pain level would be expected to increase in all patients during this period if untreated, a ΔP_{60} of +0.2 or less represents a significant analgesic response resulting from placebo administration. By using this criterion, we classified 39% of the 107 patients in the present study as placebo responders.

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Abbreviations: ΔP_{60}, change in pain 60 min after placebo administration; P, initial pain 5 min prior to placebo administration.

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In that previous study (9) with a sample of only 23 patients, ΔP_{60} appeared to be distributed bimodally with 61% of the patients reporting an increase in pain 1 hr after a placebo (placebo nonresponders), whereas 39% reported no change or a decrease in pain (placebo responders). In the present study, where the sample is much larger (107 patients), the distribution of ΔP_{60} also appeared to be bimodal with a minimum between 0 and +1 (Fig. 1). This minimum was seen with all possible combinations of bin boundaries and bin widths up to a bin width of 0.6. Thus the division of patients into two distinct apparently nonoverlapping populations on the basis of the change in pain they report after administration of a placebo does not appear to be arbitrary.

Recent results on the effects of naloxone in this experimental situation also support the conclusion that the division of patients into responder and nonresponder subpopulations is not arbitrary. High doses of naloxone (7.5 and 10 mg) are hyperalgesic with respect to placebo (9, 10). When patients are divided into responder and nonresponder populations by using the criterion discussed above, naloxone appears to have no effect on placebo nonresponders at any dose. In contrast, a high dose of naloxone causes a marked increase in the pain reported by placebo responders. In addition, a similar but analgesic effect produced by low doses of naloxone (0.4 and 2 mg) also distinguishes between responders and nonresponders (10).

If the probability of observing a placebo response were independent of the initial pain, then the mean initial pain of the responders would be indistinguishable from that of nonresponders. However, comparison of the mean value of P for the placebo responder group (4.27, SD 2.37) with that of the nonresponder group (3.16, SD 2.05), shows that the two means differ significantly ($P < 0.025$, Student t test). Thus, there appears to be a relationship between the level of pain reported by a patient prior to receiving a placebo and the likelihood of placebo analgesia. It might be argued that this difference results from the constraints of the pain measurement paradigm, because patients with very high initial pains have little latitude to report an increase in their pain after receiving a placebo. However, the highest initial pain reported was 9.1 and, because ΔP_{60}s of 0.5 or greater were taken to indicate that a patient was a nonresponder, it seems unlikely that this constraint influenced our results.

To allow a closer examination of the relationship between initial pain and the placebo response, a scattergram of ΔP_{60} vs. P was plotted (Fig. 2). The form of this scattergram is subject to at least one constraint. Because patients rated their pain on a scale of 0 to 10, the sum of P and ΔP_{60} must fall between the two values (i.e., $0 \leq P + \Delta P_{60} \leq 10$), so that the dashed lines in Fig. 2 represent the theoretical boundaries of the scattergram.

When the scattergram for the placebo nonresponders is examined, there is no obvious relationship between P and ΔP_{60} beyond that imposed by the constraints described above. However, the form of the scattergram for the placebo responders $\Delta P_{60} < 0.2$ indicates that there is a relationship between P and ΔP_{60}. Thus, there is a complete absence of points in the triangular area bounded by the P axis, the line $\Delta P_{60} + P = 0$, and the line $P = 2.6$, and in a second triangle formed by the line $\Delta P_{60} + P = 0$, the line $\Delta P_{60} = -3.2$, and the line $P = 10$. This gives the placebo-responder scattergram a steplike form with the points for $P < 2.6$ clustered around $\Delta P_{60} = 0$, whereas for $P > 2.6$, ΔP_{60} takes values as low as -3.2. It seems very unlikely that this steplike form of the scattergram could occur by chance, which suggests that there is a threshold level of pain ($P = 2.6$) below which responders report essentially no change in their pain levels after receiving a placebo, but above which significant decreases in pain are often reported.

The suggestion that there is a threshold level of pain above which the placebo response is enhanced is further supported

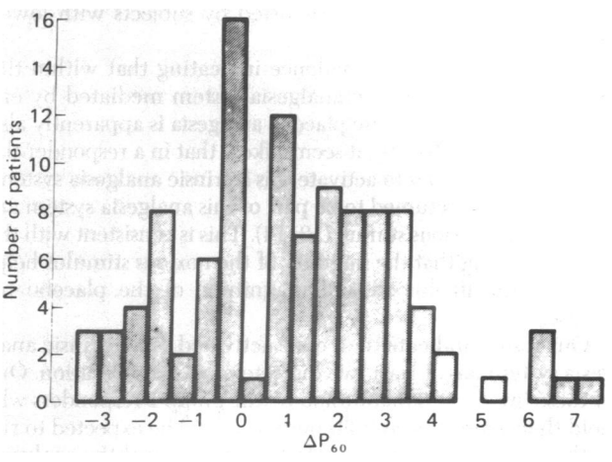

FIG. 1. Histogram showing distribution of changes in pain (ΔP_{60}) reported by 107 patients during the 60 min after administration of a placebo. Note that there is a minimum at $\Delta P_{60} = 0.5$; for further discussion see text. There is a secondary minimum at $\Delta P_{60} = -1$; see also Fig. 3.

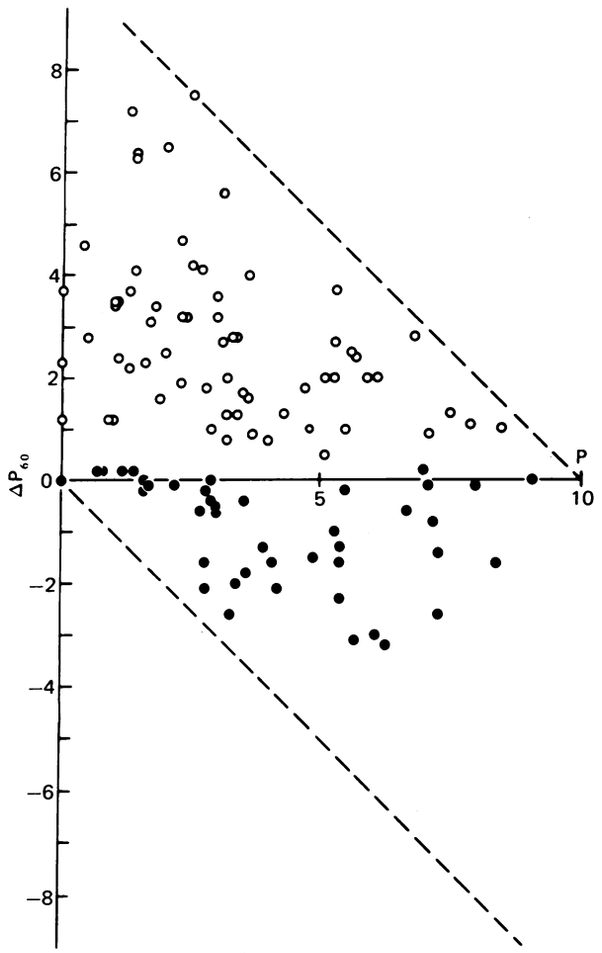

FIG. 2. Scattergram relating ΔP_{60} for each patient to his or her initial pain (P). O, Data from placebo nonresponders. ---, Limits of the scattergram; for derivation, see text. ●, Data from placebo responders; note the steplike form of the distribution of pain reports. Above the initial pain level of 2.6, there appears a group of patients whose pain decreases.

by a comparison of the proportion of responders seen having values of $P > 2.6$. Only 24% (9 of 38) of the patients with initial pain levels below 2.6 were placebo responders, whereas 49% (33 of 68) of the patients with initial pain above 2.6 were responders. This difference is significant ($P < 0.025$, χ^2 test with one degree of freedom). Thus, an increase in the initial pain above the threshold level of 2.6 can apparently cause some nonresponders to become placebo responders. This threshold accounts for the finding that placebo responders report a higher mean initial pain than nonresponders, and confirms that there is a correlation between initial pain and the probability of observing a placebo response.

The apparent step in the scattergram is due to an increase in the variability and efficacy of the placebo response. To examine these changes in more detail, a histogram of the values of ΔP_{60} when $P > 2.6$ was plotted for the placebo responders (Fig. 3). This histogram appears to be bimodal with a minimum at $\Delta P_{60} = -1$. This minimum was seen with all possible combinations of bin boundaries and bin widths up to 0.5. This suggests that when the initial pain is greater than 2.6, placebo administration can produce two distinct levels of analgesia, although a larger sample would be required to confirm this conclusion. One level involves essentially no change in pain (group 1 patients), and is similar to the analgesia reported by responders with initial pain below 2.6. The second involves a significant decrease in pain (group 2 patients). Thus, when initial pain rises above 2.6, a subpopulation of placebo responders who report additional analgesia is revealed. Indeed, because the proportion of group 1 patients with initial pain above 2.6 did not differ significantly from the proportion of such patients with initial pain below 2.6 ($P > 0.2$, χ^2 test, one degree of freedom), the increased proportion of placebo responders seen for $P > 2.6$ can be wholly accounted for by the appearance of the group 2 placebo responders.

The finding that a subpopulation of placebo responders (group 1 responders) report virtually no change in their pain 1 hr after administration of a placebo suggests that, under conditions in which the pain level is normally increasing, such patients respond to a placebo by holding their pain constant. It could also be postulated that at least some group 1 responders experience a decrease in pain immediately after administration of a placebo and then show a rise in pain, so that the report of zero change is an artifact. The former hypothesis was confirmed when the time course of the mean change in pain after administration of a placebo was examined for each type of patient

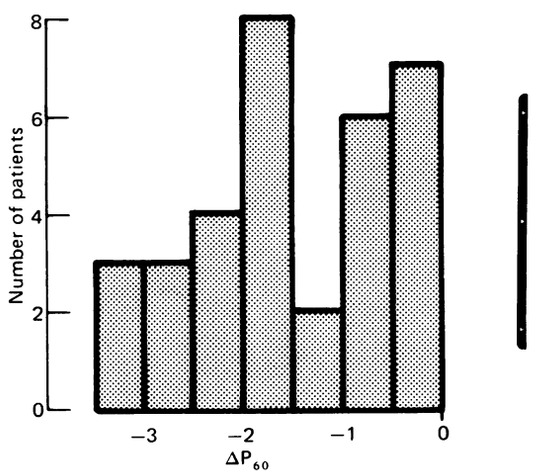

FIG. 3. Histogram of values of ΔP_{60} for those placebo responders with initial pains greater than 2.6. The histogram is bimodal with a minimum at $\Delta P_{60} = -1$ (the secondary minimum of Fig. 1).

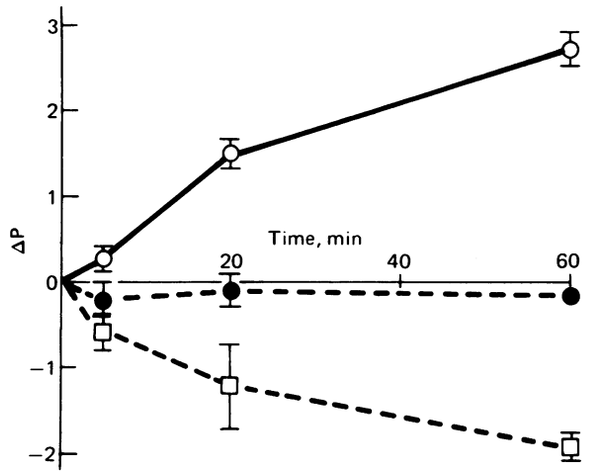

FIG. 4. Time course of mean change in pain after placebo administration for the nonresponders (○), group 1 responders (●), and group 2 responders (□). The error bars represent SEM. Note that the SEM for change in pain reported after 60 min by group 1 responders was so small (±0.06) that it could not be shown.

(Fig. 4). Whereas the mean pain level reported by nonresponders increased significantly between each measurement, group 1 responders showed no significant change at any point. In contrast, group 2 responders reported a mean decrease in pain at each time point.

DISCUSSION

The present results extend our previous report indicating that patients fall into distinct groups after placebo administration (9). With this clinical paradigm, all untreated patients had steadily increasing pain. In contrast, after taking the placebo, a significant number report that their pain either remained unchanged or decreased (placebo responders). That placebo responders differ qualitatively from nonresponders is suggested by the separation of distributions of pain reports, as well as by the differing actions of naloxone on the two groups (9, 10).

The present results indicate that the initial level of pain influences the analgesic response to a placebo. Thus, a subject with initial pain above threshold level is more likely to report analgesia after taking a placebo than one with initial pain below this level. Furthermore, the mean level of analgesia reported by those subjects whose initial pain exceeds the threshold is considerably greater than that reported by subjects with lower initial pain.

There is considerable evidence indicating that within the brain there is an intrinsic analgesia system mediated by endorphins (11, 12). Because placebo analgesia is apparently also endorphin-mediated (9), it seems likely that in a responder the effect of a placebo is to activate this intrinsic analgesia system. Some neurons presumed to be part of this analgesia system are activated by noxious stimuli (13, 14). This is consistent with the present finding that the intensity of the noxious stimulus helps set both the likelihood and magnitude of the placebo response.

Our results indicate that, once activated, the intrinsic analgesia system has at least two discrete modes of operation. One of these (mode 1) is manifested by the group 1 responders who hold their pain constant although it would be expected to rise in the absence of a placebo. Mode 1 operation of the analgesia system can be triggered at all initial pain levels, and thus it appears that the probability of triggering mode 1 is independent of the ongoing pain level. The second mode of operation (mode 2) is manifested by the group 2 responders whose reported pain

falls steadily for at least 1 hr after placebo administration. Mode 2 operation can be triggered only when initial pain is above the threshold level of 2.6, which suggests that to trigger it a minimal level of activity in the ascending pain transmission pathway is required. Furthermore, because the magnitude of the analgesia reported by group 2 responders is apparently *independent* of initial pain once the threshold is exceeded, it seems likely that mode 2 operation of the system produces a set degree of analgesia.

One conclusion of the present work is that studies of analgesic effectiveness that employ placebo will be significantly influenced by the nature and severity of the pain being studied. Studies of experimental pain commonly measure a shift in the strength of the stimulus required to cause a just-perceptible pain (pain threshold). This pain threshold would be represented by a value at the low end of our pain scale. With such low initial pain severity, a placebo response is less likely to occur and, when it does, its magnitude will be small. Because such studies would tend to underestimate the magnitude and extent of placebo analgesia, it is not surprising that placebo produces significant analgesia in only 3% of experimental subjects compared to about 36% of patients with clinical pain.

Our results support the hypothesis that the severity of the pain being treated influences the response to placebo administration. However, even patients reporting high initial pain levels have only a 50% chance of obtaining placebo analgesia. There are thus other factors that significantly influence placebo analgesia.

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