the acute form of the disease occurs in the second or third trimester of pregnancy or within 2 months after delivery. Most children infected during the perinatal period become persistent carriers.

Treatment of the carrier state of hepatitis B virus is important since the carrier state is associated with varying degrees of liver damage and poses a major public health danger. Treatment with interferon is currently receiving considerable attention and some of the results are promising. Antiviral drugs such as adenine arabinoside, alone or in combination with interferon or other agents, appear useful and may provide the means of treating severe chronic hepatitis B infection.

Finally, this outbreak among the non-human primates illustrates the value of surveillance and of strict observance of a safety code of practice in prevention of transmission of the infection. In the absence of a controlled study it is not possible to ascribe any particular role to the use of hepatitis B immunoglobulin in limiting the spread of this infection to the human handlers of these chimpanzees. Nevertheless, it should be stressed that even before immunoglobulin was given, none of the staff became infected with hepatitis B virus although the strain, $a_2$ldw, is identical with human strains and the keepers were previously in very close contact with the chimpanzees.

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THE MECHANISM OF PLACEBO ANALGESIA

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Summary The effect of naloxone on dental postoperative pain was studied to examine the hypothesis that endorphins mediate placebo analgesia. All patients had extraction of impacted mandibular third molars with diazepam, N_2O, and local block with mepivacaine. 3 h and 4 h after surgery naloxone or a placebo was given under randomised, double-blind conditions. Pain was evaluated on a visual analogue scale. Patients given naloxone reported significantly greater pain than those given placebo. Patients given placebo as their first drug were either placebo responders, whose pain was reduced or unchanged, or nonresponders whose pain increased. Naloxone given as a second drug produced no additional increase in pain levels in nonresponders but did increase pain levels of placebo responders. Nonresponders had a final mean pain rating identical to that of responders who received naloxone as their second drug. Thus the enhancement of reported pain produced by naloxone can be entirely accounted for by its effect on placebo responders. These data are consistent with the hypothesis that endorphin release mediates placebo analgesia for dental postoperative pain.

Introduction

IN a variety of painful conditions a remarkably constant proportion (about one third) of patients obtain significant relief from a placebo.[1] Almost nothing is known about what causes placebo effects but the recently discovered endogenous opiate-like substances (endorphins) seem likely to be involved. The analgesic placebo effect and narcotic analgesia appear to have a similar mechanism. With repeated use over longer periods placebo analgesia becomes less effective (tolerance), there is a compulsion to continue taking placebo with a tendency to increase "dose" over time, and an abstinence syndrome appears when placebo is suddenly withdrawn.[2–4] Placebo may partially reverse withdrawal symptoms in narcotic addicts,[5] and people who respond to placebos get significantly more relief from postoperative pain with narcotic analgesics.[1,6–9]

If placebo-induced analgesia is mediated by endorphins then naloxone, a pure opiate antagonist, would be expected to block it. The early observation by Lasagna that 8 mg of naloxone produced less analgesia than placebo[10] supports this hypothesis. In this study we investigated the direct effect of naloxone upon placebo-induced analgesia.

Patients

The patients were 27 males and 24 females with ages ranging from the late teens to early thirties. 47 patients were from the private practice and 4 from the clinic of the department of oral surgery. Subjects were healthy except for impacted wisdom teeth. Oral consent and written consent on forms following the guidelines of our campus committee on human experimentation were obtained. Patients were told that they might receive either morphine, placebo, or naloxone (an agent that might increase their pain). In previous double-blind studies, telling patients that they might receive placebo did not inhibit the placebo response.[11–13]

Methods

Patients received 10–20 mg intravenous diazepam. Nitrous oxide (N_2O) (15–40%) was inhaled and mepivacaine (3% without vasoconstrictor), a local anæsthetic effective for 45–75 min, was used to block the mandibular and long buccal nerves.[1–4] Impacted mandibular third molars were removed with a standardised technique and all surgery was done by N. G. After surgery, N_2O was stopped, and after 100% oxygen for 10 min, patients were transferred to a nearby recovery room for continued observation, where they were given experimental drugs and pain was measured. Patients were randomly placed in experimental groups by selecting a coded envelope. Experimental drugs were delivered in equal volumes as a bolus via an intravenous catheter and were given double-blind. No codes were broken during any experiment.

Two pain-rating scales were used:[14] the visual analogue scale, a 10 cm horizontal line on 8×10 in (203×254 mm) white paper, had "no pain" printed at the left end and "worst pain ever" at the right end. Patients were asked to make a mark crossing this line at a point representing the intensity of their pain. A separate card was given for each rating and patients could not refer back to their previous ratings. Beginning at the second pain rating, a second, verbal, rating was requested in order to check the reliability of the first. On the verbal scale, patients indicated whether their pain had increased, decreased, or remained the same since the last time they rated their pain level. For more than 95% of measurements the change in the visual analogue scale correlated with the verbal scale. When the pain was rated as unchanged on the verbal scale 50% of the visual analogue scale ratings were within ±2 mm of the previous score and 92% were within ±10 mm.

The times when pain was rated and drugs were given are shown by the data points in the figures. Drugs were given at 2 h (drug 1, D_1) and 3 h (drug 2, D_2), respectively, after the start of anæsthesia (zero time) as determined by paræsthesiæ and sensory testing of analgesia. All patients were given 10 mg naloxone (Endo Laboratories) or an identical volume of naloxone vehicle (placebo) or morphine sulphate (7·5 mg) each time. 17 patients received placebo as D_1 and D_2; 23 patients received placebo as D_1 and naloxone as D_2; and 11 patients received naloxone as D_1 and placebo as D_2. 5 patients dropped out of the study.

Results

The patients were randomly given morphine, placebo, or naloxone (the combination of morphine followed by naloxone being excluded) so that patients could expect a powerful analgesic as well as something which might make pain worse. Patients given morphine were excluded from the subsequent analysis of the results.

As part of the consent form, patients were permitted to withdraw from the experiment. 5 did so before the final pain determination, presumably because they had reached the limit of pain tolerance, although analysis of the 8 data points (out of a possible 9) does not suggest that these patients differed from those who completed the study.

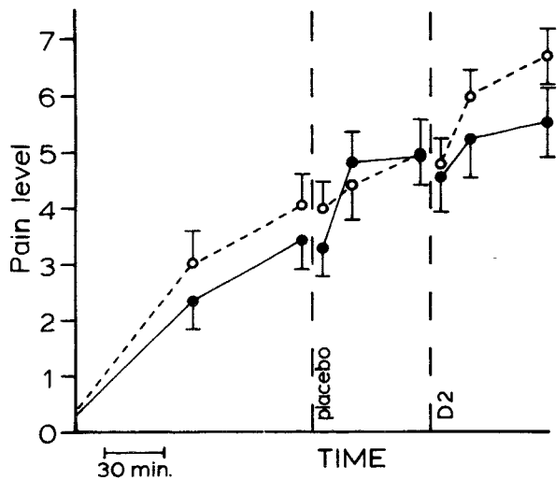

Fig. 1—The effect of naloxone on pain.

Time was measured from the start of anæsthesia. Both patient groups were given placebo as their first drug. The administration of the second drug is denoted by D_2. ● mean (±S.E.) pain ratings for patients given placebo as a second drug (n=17); o mean pain ratings for patients given 10 mg naloxone as a second drug (n=23). Difference during the three immediately postoperative hours was insignificant The group given naloxone had significantly greater mean pain ratings 1 h after its administration ($P<0·05$ by t test).

Naloxone Enhancement of Pain

We compared the effect of naloxone and placebo in patients given placebo as D_1 and either naloxone or

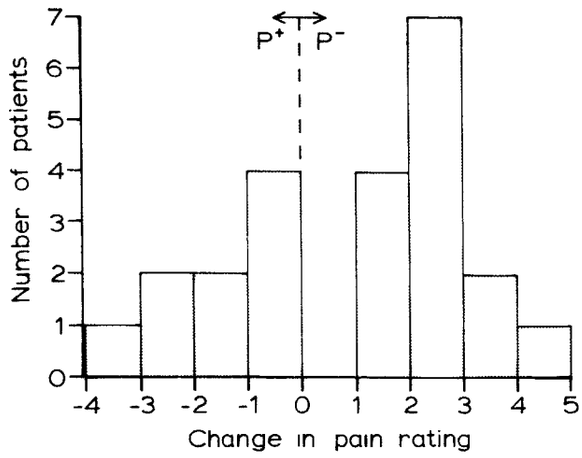

Fig. 2—Change in pain 1 h after placebo compared with pain rating 5 min before placebo.

P^+ and P^- indicate the placebo responders and nonresponders, respectively. A bimodal distribution is apparent.

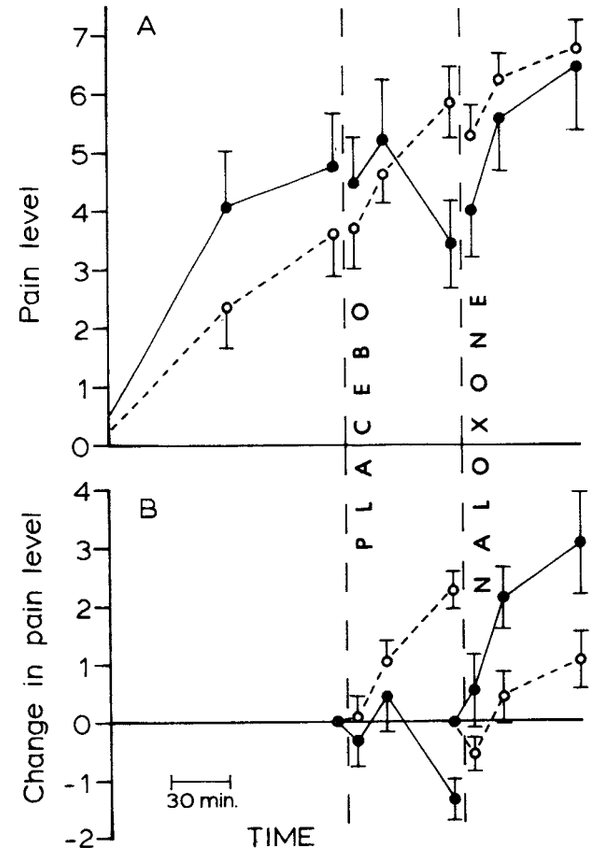

Fig. 3—Differential effect of naloxone on placebo responders and nonresponders.

All patients received placebo as the first drug and naloxone as the second.

Upper graph: mean pain levels for placebo responders (●) (n=9) and nonresponders (o) (n=14) are plotted. After naloxone, the difference in mean pain level for these two groups becomes insignificant.

Lower graph: cumulative change in pain level compared with 5 min before the drug was given (data from upper curve). After naloxone the change in pain level is greater in positive placebo responders. A significant difference is apparent 5 min after naloxone ($P<0·05$ by t test), and is greater 20 and 60 min after naloxone ($P<0·125$). The latency of the placebo effect seems to be less than 5 min.

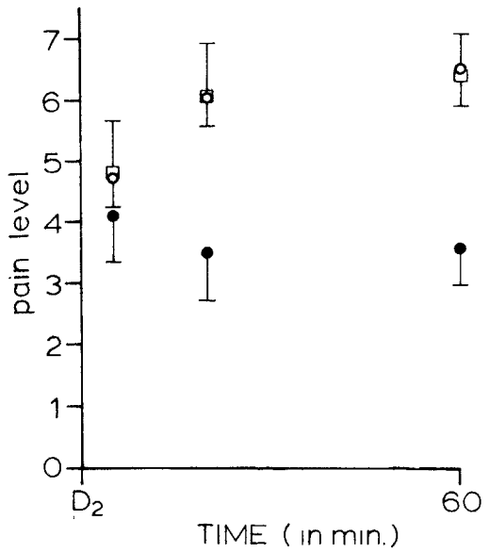

Fig. 4—Absence of naloxone effect in placebo nonresponders: pain ratings during the hour after the second drug was given.

o patients given placebo followed by naloxone (n=23); □ patients given placebo followed by a second placebo to which they did not respond (n=6); ● patients given placebo followed by a second placebo to which they did respond (n=11).

placebo as D_2. 5 min before and 1 h after giving of placebo as D_1, the pain ratings of patients in each group did not differ significantly (fig. 1). Throughout the measurement period, there was a rise in the mean pain level reported. However, 1 h after D_2 was given, the group given naloxone reported significantly more pain than the group given a second placebo.

Comparison of Placebo Responders and Nonresponders

In this study, placebo responders were defined as patients whose pain rating 1 h after taking placebo remained constant or decreased compared with their rating 5 min before they took it. Placebo nonresponders were those whose pain was greater 1 h after placebo. By this definition, when placebo was given as D_1, 39% of patients were responders. The bimodal distribution of change in pain observed 1 h after placebo as D_1 indicates that this distinction between responders and nonresponders is not arbitrary (fig. 2).

Patients receiving placebo as D_1 were divided into responders and nonresponders in order to compare naloxone's differential effect on the two patient groups. Naloxone enhanced pain ratings much more in placebo responders (fig. 3), bringing their mean pain rating to the same level as that of nonresponders. This convergence suggested that most, if not all, the analgesic effect of placebo is naloxone-reversible, a conclusion supported by the observation that naloxone had no obvious effect upon placebo nonresponders. Fig. 4 shows that the time-course and final pain level were the same for placebo nonresponders and patients receiving naloxone.

Magnitude and Time Course of Effect

Except during the recovery period, mean pain ratings during the experiment were well within ±2 cm of the middle of the visual analogue scale (fig. 3) which suggests that the scale was appropriate to the pain levels experienced. The difference in final mean levels between placebo responders (3·5) and nonresponders (6·5) (fig. 4) is almost the full range of mean pain levels in fig. 3. The mean pain rating for nonresponders was almost double that of responders, indicating that the placebo effect, when present, was quite large. The increase in pain caused by naloxone was also quite large.

Enhancement of pain ratings in placebo responders was significantly greater than in nonresponders as early as 5 min after naloxone was given ($P<0·05$) (fig. 3, lower graph). This naloxone enhancement was greater after 20 min but appeared to level off at 60 min (fig. 4). Thus the peak of the placebo effect was later than 20 min and its duration was greater than 1 h, a time course consistent with that observed by others for analgesic placebo.[15]

5 of 14 patients given placebo as both D_1 and D_2 responded to the second placebo. If naloxone was given first, the number of responders dropped to 2 of 11. This difference, although not statistically significant, suggested that giving naloxone first reduced the probability that a patient would be a positive placebo responder.

Discussion

This study supports the hypothesis that endorphin activity accounts for placebo analgesia, first because naloxone causes a significantly greater increase in pain ratings in placebo responders than in nonresponders, and second because prior administration of naloxone reduces the probability of a positive placebo response.

The observation that placebo nonresponders have almost the same postoperative pain levels as those receiving naloxone suggests that the enhancement of pain by naloxone can be completely accounted for by an action on placebo responders. If naloxone had had a pain-enhancing action independent of the placebo response naloxone would have increased pain even in placebo responders. That it did not, even with the large dose of naloxone (10 mg) employed, supports to the conclusion that the placebo effect is endorphin-mediated.

4 of the 5 patients who prematurely dropped out of the study had received naloxone as the second drug, and they dropped out between the 20 and 60 min pain ratings after naloxone. In this group the pain rating at the time of termination (mean 6·4) was almost identical to the 60 min rating of the patients who continued in the experiment and who had either received naloxone or were placebo nonresponders to the second drug. This preliminary observation suggests that a patient's ability to tolerate pain is, to some degree, separable from his own perception of its intensity.

Naloxone is a specific opiate antagonist and, in the dose employed in this study, has no known effect when administered to opiate-naive subjects.[16,17] Although no patient received narcotics before participation in the experiment, diazepam and N_2O were given before surgery. Naloxone reverses the effect of 67% N_2O on tail flick in the rat[18] but in this study measurements were made 1–3 h after N_2O, when the amount left in the body is minimal. Diazepam is not an effective analgesic, although it may work synergistically with narcotics to enhance analgesia. In animals diazepam and opiates act upon independent neural systems.[19,20] More impor-

tantly, all patients receiving diazepam and N_2O so that the difference in naloxone effects between placebo responders and nonresponders could not be explained simply by a selective antagonism of naloxone towards these two drugs or to systemically absorbed local anæsthetic. Furthermore, the N_2O, diazepam, and mepivicaine levels fell during the measurement period while the effect of naloxone increased with time, being greatest 1 h after being given. Although this is relatively late compared with the reversal of narcotic overdose (which occurs within 2 min of intravenous administration) the peak for naloxone blockade of stimulation-produced analgesia in cats is 30–40 min after injection and may last several hours.[20] This prolonged time-course is also consistent with our observation that the proportion of positive responders is reduced when placebo is given an hour after naloxone.

In our experiments, a relatively homogenous group of patients were operated upon with a standardised procedure. Interestingly, the mean pain ratings were almost identical in patients given naloxone and those who did not respond to placebo (figs. 3 and 4), which may mean that part of the variability in pain intensity reported by patients who all have similar lesions may be due to differences in endorphin activity.

In contrast to our previous results,[14] investigators using experimental noxious stimulation have either failed to find pain enhancement with naloxone[21,22] or have shown mixed effects in unselected subjects.[23] It is not clear why our clinical paradigm revealed naloxone hyperalgesia while experimental paradigms did not. Perhaps the prolonged duration of the pain or the added stress of the clinical situation accounts for this difference. That stress may be a factor is indicated by the strong positive correlation between plasma levels of adrenocorticotrophin (a stress indicator) and endorphins.[24] Recently, an endogenous pain-suppression system has been described which can be activated by electrical stimulation of the brain or by systemically administered opiates.[25,26] In patients with chronically implanted electrodes naloxone-reversible relief of clinical pain has been produced with only minimal effects on experimental pain thresholds.[28] Conceivably, the analgesic effect of placebo upon clinical pain results from activation of the same pain-suppression system.

If, as the present study suggests, the analgesic effect of placebo is based on the action of endorphins, future research can proceed with an analysis of variables affecting endorphin activity rather than simply recording behavioural manifestations of placebo effects. Greater understanding of endogenous mechanisms of analgesia should lead to more effective management of clinical pain with a combination of pharmacological, behavioural, and physical methods.

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References at foot of next column

REPEATED FAILURE OF NICKEL-CONTAINING PROSTHETIC HEART VALVES IN A PATIENT ALLERGIC TO NICKEL

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Summary Life-threatening peri-prosthetic incompetence developed with two successive nickel-containing mitral-valve prostheses in a patient allergic to nickel. Neither prosthesis had been incorporated satisfactorily. Her present nickel-free prosthesis seems to be satisfactory 22 months after insertion. Since allergy to nickel may have been involved in the failure of these prostheses, it is recommended that nickel-sensitive patients should be given nickel-free prostheses.

Introduction

SEVERAL thousand prosthetic heart valves are implanted in patients with end-stage rheumatic heart-disease each year in the U.K. Although new cases of rheumatic endocarditis are now uncommon in developed countries, many patients with damaged valves still present for replacement surgery, and heart-valve replacement is likely to continue to form a large proportion of the cardiac surgical workload over the next 10–20 years.

With the exception of the Lillehei-Kaster prosthesis, all the commonly used valve prostheses or bio-prostheses contain nickel in the alloy which forms the metal framework. Yet, although allergy to nickel is common, there are no reports of failure of valve prostheses attributed to this cause.

The following case-report details the sequence of prosthetic-valve failures in a patient with allergy to nickel, whose early course we have already reported.[1]

Case-report

A woman born in 1914, who first presented in 1963 with a

DR LEVINE AND OTHERS: REFERENCES

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