Br. J. clin. Pharmac. (1983), **15**, 221–226

EFFECTS OF NALOXONE ON POST-OPERATIVE PAIN AND STEROID-INDUCED ANALGESIA

P. SKJELBRED
Department of Oral Surgery and Oral Medicine, and
Institute of Pharmacology, University of Oslo, Norway

P. LØKKEN
Institute of Pharmacology, University of Oslo, Norway

1 In a controlled crossover study identical oral surgical procedures were performed on two separate occasions in six patients.

2 Two h after surgery, either 40 mg methylprednisolone (Solu-Medrol®) or placebo (saline) was administered intravenously in a double-blind randomized fashion.

3 Five h after surgery, three patients received 4 mg naloxone (Nalonee®) while three patients received placebo (saline) intravenously, followed by a crossover to alternative injections 1 h thereafter.

4 Several measurements/assessments were recorded for a paired comparison of the post-operative courses.

5 The mean pain assessment (VAS) was reduced by about 50% 45 min after the steroid injection ($P = 0.03$).

6 Neither increasement of the post-operative pain nor reversal of the steroid-induced analgesia could be demonstrated by injection of 4 mg naloxone.

7 Swelling was reduced by 46% on day 3 after the operation when the steroid was injected as compared to placebo ($P = 0.06$); on day 6 the reduction averaged 60% ($P = 0.04$).

8 According to overall assessments after the second operation all patients expressed clear preference for the post-operative course when the steroid was injected.

9 Present and previous results in this model with bilateral oral surgery suggest that short term corticosteroid administration deserves attention as an efficient means which may be of value in reducing pain and excessive inflammation in surgery and traumatology.

Introduction

Naloxone has been reported to induce hyperalgesia in placebo responders with pain after oral surgery (Levine *et al.*, 1978; Levine *et al.*, 1978). There has been some criticism, however, regarding the experimental design of these studies (Skrabanek, 1978; Korczyn, 1978; Goldstein & Grevert, 1978). Various investigators have reported conflicting findings regarding the pain-intensifying effect of naloxone in tests with experimental nociception in animals or humans (for reference see Pert, 1980). Levine *et al.* (1978) suggested that endorphin activity accounts for placebo analgesia, and that perhaps the added stress of the clinical situation may explain different findings in humans with experimental and clinical pain. In patients with acute stress after abdominal surgery, a parallel increase was demonstrated in plasma β-endorphin and cortisol levels, and it was concluded that the study provided additional evidence linking plasma β-endorphin to the hypothalamic-pituitary-adrenal axis (Dubois *et al.*, 1981). A functional involvement of glucocorticoids in opioid actions is also supported by findings in animals (Chatterjee *et al.*, 1982).

In controlled crossover studies on patients who underwent bilateral oral surgery, a highly significant steroid-induced pain reduction was found, either 9 mg betamethasone (Celeston Chronodose®) was administered intramuscularly before (Skjelbred & Løkken, 1982a) or 3 h after one operation (Skjelbred & Løkken, 1982b), and compared to placebo injected at the contralateral operation. In both trials about 50% reduction in the mean pain assessments (visual

0306–5251/83/0200–2210 $02.00

analogue scale) was observed 3 h after the steroid injections, and of the 36 patients involved, 35 preferred this treatment course. Since most steroid-induced actions have a latency of onset (Flower, 1978), it was of interest to note that some patients reported definite pain relief within minutes after the steroid injection (Skjelbred & Løkken, 1982b), while with others there was a time lag. This may, at least in part, reflect variations in the rate of absorption from the intramuscular site of injection. Activation of an opioid pain-suppressive system might possibly account for this steroid-induced analgesia. If so, the system would be expected to be disrupted by naloxone.

The present study examines effects of naloxone on post-operative pain and steroid-induced analgesia. A further aim is to study the efficiency of a single intravenous corticosteroid injection in reducing pain and modulating a post-operative course.

Methods

Patients

The trial included six healthy volunteers, five females and one male (mean age 21 years, range 19–22 years). They were all in need of prophylactic surgical removal of bilateral, asymptomatic, impacted third molar teeth of similar shape and position, as evaluated clinically and by means of orthopantomograms. The patients were informed about the implications of the trial and that the drugs given on the day of operation might reduce, increase or leave their pain unaffected; further that they were free to withdraw their consent to participation at any time. There was, however, no withdrawal or drop-out.

Drugs

Each patient received the same amount of local anaesthetic (Carbocain Dental®, Astra) at both operations, five patients 5.4 ml and one 3.6 ml.

Two h after surgery an intravenous line was established by means of an i.v. cannula (Venflon®) and continuous 0.9% saline infusion. Either 40 mg methylprednisolone (1 ml Solu-Medrol®, Upjohn) or placebo (saline) was then administered intravenously. These injections were given on a double-blind crossover basis, and allocated according to a randomization list, so that half of the patients received methylprednisolone at the first operation. In order to keep double-blindness, these injections were given by a nurse with no other involvement in the trial. Three h later patient numbers 1, 2 and 3 received 4 mg naloxone (10 ml Nalonee®, Winthrop), while patient numbers 4, 5 and 6 received placebo (10 ml saline) intravenously, followed by a crossover to alternative injections 1 h thereafter (Figure 1). The patients left the clinic 7 h after completion of surgery and were then supplied with and allowed to take 0.5 g paracetamol tablets (Panodil®, Winthrop) if greatly needed. The intake was recorded. No other drugs were permitted during the 10 day before each operation or during the post-operative observation period.

Operations

The operations were performed as previously described (Løkken & Skjelbred, 1980), with an interval of 14 days. The mean duration of the operations was 9.5 min (range 6–13 min) when the corticosteroid was given and 9.0 min (range 7–13 min) when placebo was given.

Assessments/statistical analyses

Pain was rated on a visual analogue scale with lines that ran from 'no pain' (0 mm) to 'pain cannot be worse' (100 mm). Pain was assessed immediately after completion of surgery, then at 30 min intervals for the next hour. Between the second and eighth post-operative h pain was assessed each 15 min, then at 30 min intervals for the following 1.5 h. Pain was further assessed at bedtime that day of operation, and at bedtime the following 5 days.

Other measurements/assessments recorded for a paired comparison of the post-operative courses were swelling in the jaw region, mouth-opening ability, local temperature, bleeding, haematoma/ecchymosis, wound healing, and complaints related to the medication (Løkken & Skjelbred, 1980). After the second operation the patients gave an overall assessment of the course after this operation compared with the previous one by means of a visual analogue scale with lines that ran from 0 mm (no difference) upwards to 100 mm (maximal preference for the last course) and downwards to 100 mm (maximal preference for the previous course) (Skjelbred & Løkken, 1982c).

Statistical analyses were performed with a two-sided Wilcoxon signed rank test with correction for ties (Lehmann & d'Abrera, 1975). A significance level of 5% was used.

Results

Pain

The steroid injection was followed by a marked reduction in pain (Figure 1). Although there were considerable individual variations in the response, the difference in pain assessments reached a level of significance in favour of the steroid 45 min after the injection ($P = 0.03$).

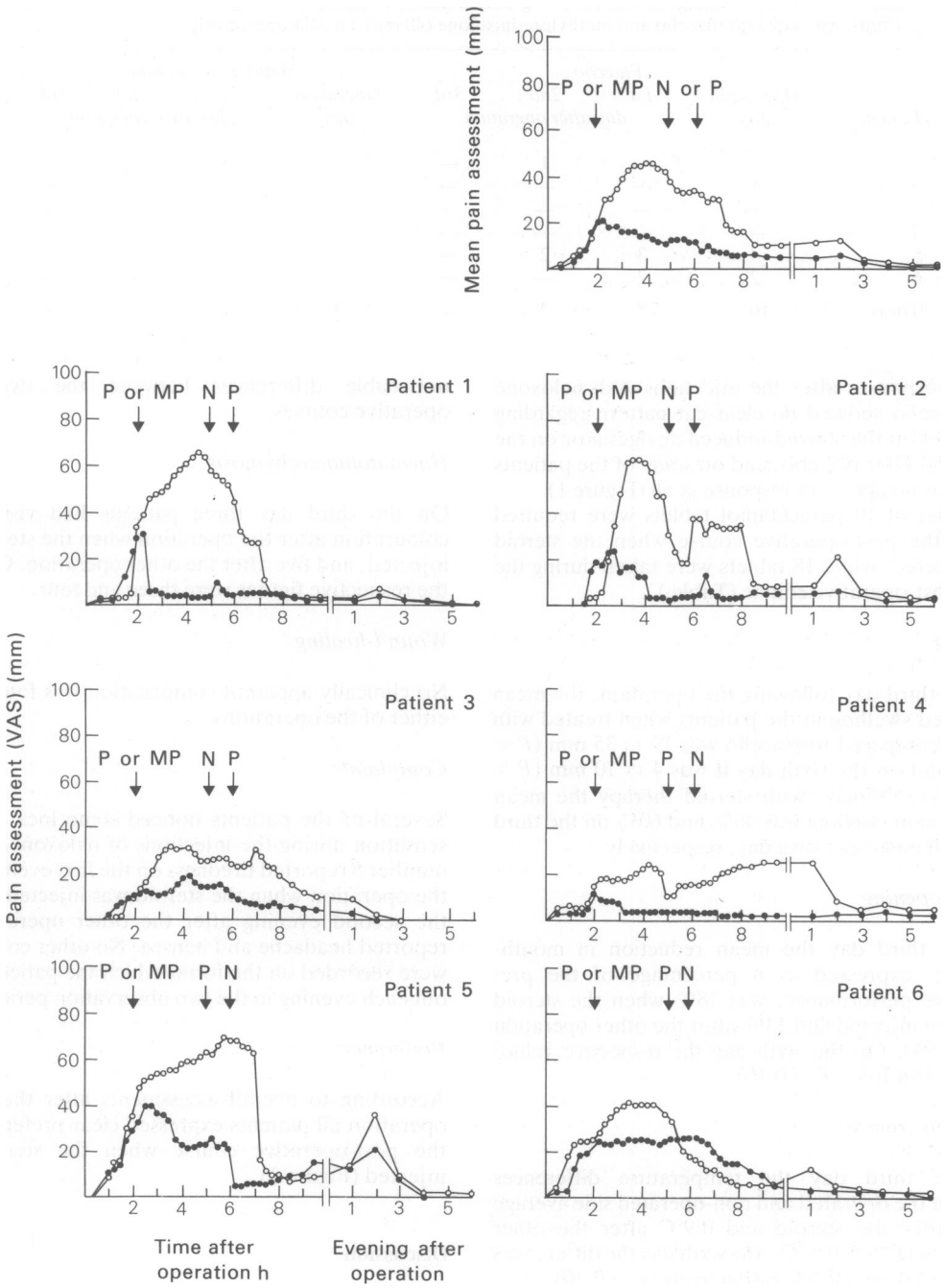

Figure 1 Pain assessments in six patients comparing i.v. injections of placebo (○) and 40 mg methylprednisolone (●) 2 h after two identical surgical procedures. The figure further shows the effects on pain and steroid-induced analgesia by injections of 4 mg naloxone (N) or placebo (P) 5 and 6 h after surgery.

Table 1 Number of analgesic tablets (0.5 g paracetamol) required after bilateral oral surgery in six patients injected with placebo and methylprednisolone (40 mg) 2 h post-operatively.

	Placebo				*Methylprednisolone*			
Patient	*Operation day*	*1st day after operation*	*2nd day after operation*	*3rd day after operation*	*Operation day*	*1st day after operation*	*2nd day after operation*	*3rd day after operation*
1	3	—	1	—	—	2	—	—
2	1	—	—	—	—	—	—	—
3	—	—	—	—	—	—	—	—
4	—	—	—	—	—	—	—	—
5	4	3	2	—	2	3	—	—
6	2	2	—	—	1	2	—	—
Total	10	5	3	—	3	7	—	—

The responses after the injections with naloxone and placebo showed no clear-cut pattern regarding the effect on the steroid-induced analgesia or on the pain level after placebo, and on some of the patients there was no apparent response at all (Figure 1).

A total of 10 paracetamol tablets were required during the post-operative course when the steroid was injected, while 18 tablets were taken during the other post-operative course (Table 1).

Swelling

On the third day following the operation, the mean measured swelling in the patients when treated with steroid compared to placebo was 19 *vs* 35 mm ($P = 0.06$), and on the sixth day it was 4 *vs* 10 mm ($P = 0.04$). Accordingly, with steroid therapy the mean reduction in swelling was 46% and 60% on the third and sixth post-operative day, respectively.

Mouth-opening

On the third day the mean reduction in mouth-opening, expressed as a percentage of the pre-operative performance, was 18% when the steroid had been injected and 34% after the other operation ($P = 0.04$). On the sixth day the respective values were 12 and 16% ($P > 0.10$).

Oral temperature

On the third day the temperature differences between the operated and non-operated side average 0.4°C after the steroid and 0.9°C after the other operation ($P > 0.10$). On the sixth day the differences were −0.1°C and 0.6°C respectively ($P > 0.10$).

Bleeding

Bleeding episodes were not reported following either of the operations, and assessments 4 h post-operatively and just before bedtime on each of the six consecutive evenings after surgery, did not reveal any noticeable differences between the two post-operative courses.

Haematoma/ecchymosis

On the third day three patients had visible discolouration after the operation when the steroid was injected, and five after the other operation. On day 6 the respective figures were three and four.

Wound-healing

No clinically apparent complication was found after either of the operations.

Complaints

Several of the patients noticed some local burning sensation during the injections of naloxone. Patient number 5 reported tiredness on the first evening after the operation when the steroid was injected, and on the second evening after the other operation she reported headache and nausea. No other complaints were recorded on the forms which the patients filled out each evening in the two observation periods.

Preference

According to overall assessments after the second operation all patients expressed clear preference for the post-operative course when the steroid was injected (Figure 2).

Discussion

By intravenous injection of 4 mg naloxone, neither increasement of the post-operative pain nor reversal of the steroid-induced analgesia could be demonstrated in the present patients. The trial thus failed to support involvement of an endorphin system activated by clinical stress or the corticosteroid injected. The results should be cautionally interpreted. Statistical

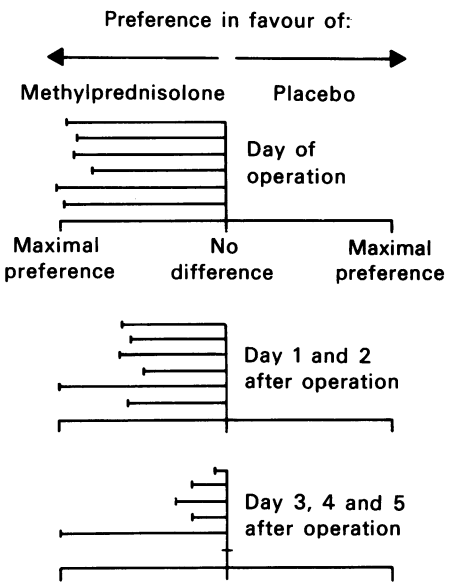

Figure 2 Preference for post-operative course in six patients comparing injections with placebo and 40 mg methylprednisolone 2 h after surgery.

considerations of the low power of this trial, including only six patients, make it difficult to detect small differences. The effects of naloxone may be quite subtle and its potential to induce hyperalgesia may depend on a multitude of factors including the dosage of naloxone, the test situation, and whether the subject is pain sensitive or not (Levine *et al.*, 1979; Pert, 1980). Apparently, none of the present patients were typical placebo responders (Figure 1). With regard to the marked corticosteroid-induced analgesia, it should be kept in mind that the control of nociception also involves pain suppressive systems which are not antagonized by naloxone (Pert, 1980; Jacob & Ramabadran, 1981). Some of these systems may have been activated by the steroid. Another possibility is that the pain relief is secondary to the anti-inflammatory effects of the steroid. Since most steroid-induced actions have a latency of onset (Flower, 1978), it is noticeable that significant pain relief was obtained within 45 min after the injection.

Besides resulting in an impressive pain relief, intravenous injection of 40 mg methylprednisolone (equals about 200 mg cortisol) 2 h after completion of surgery was followed by a significant reduction in the post-operative swelling. Compared to the measurements with placebo this reduction averaged 46% on the third day. The reduction obtained by this administration is of the same magnitude as that previously found in this model when 9 mg betamethasone (equals about 300 mg cortisol) was injected intramuscularly in a suspension which gives sustained effect (Celeston Chronodose®). Then the corresponding reduction in swelling averaged 55% (n = 24) when betamethasone was injected just before surgery (Skjebred & Løkken, 1982a) and 47% (n = 12) when the drug was injected 3 h after surgery (Skjelbred & Løkken, 1982b).

As in our two previous trials with corticosteroids, the overall assessments of the patients were clearly in favour of the post-operative course when the corticosteroid was administered (Figure 2). The trial adds further support to the view, that short term corticosteroid administration may represent an efficient and valuable means of reducing both pain and excessive inflammation in surgery and traumatology.

The authors are grateful to Leiv Sandvik, M.Sc. for performing the statistical analyses.

References

CHATTERJEE, T.K., DAS, S., BANERJEE, P. & GHOSH, J.J. (1982). Possible physiological role of adrenal and gonodal steroids in morphine analgesia. *Eur. J. Pharmac.*, **77**, 119–123.

DUBOIS, M., PICKAR, D., COHEN, M.R., ROTH, Y.F., NACNAMARA, T. & BUNNEY, Jr., W.E. (1981). Surgical stress in humans is accompanied by an increase in plasma beta-endorphin immunoreactivity. *Life Sci.*, **29**, 1249–1254.

FLOWER, R. (1978). Steroidal antiinflammatory drugs as inhibitors of phospholipase A_2. *Adv. Prostaglandin Thromboxane Res.*, **3**, 105–112.

GOLDSTEIN, A. & GREVERT, P. (1978). Placebo analgesia, endorphins, and naloxone. *Lancet.*, **ii**, 1385.

JACOB, J.J. & RAMABADRAN, K. (1981). Role of opiate receptors and endogenous ligands in nociception. *Pharmac. Ther.*, **14**, 177–196.

KORCZYN, A.D. (1978). Mechanism of placebo analgesia. *Lancet*, **ii**, 1304–1305.

LEHMANN, E.L. & d'ABRERA, H.J.M. (1975). Nonparametrics: *Statistical methods based on ranks*, pp. 129–131. San Francisco: Holden-Day Inc.

LEVINE, J.D., GORDON, N.C. & FIELDS, H.L. (1978). The mechanism of placebo analgesia. *Lancet*, **ii**, 654–657.

LEVINE, J.D., GORDON, N.C. & FIELDS, H.L. (1979). Naloxone dose dependently produces analgesia and hyperalgesia in postoperative pain. *Nature*, **278**, 740–741.

LEVINE, J.D., GORDON, N.C., JONES, R.T. & FIELDS, H.L. (1978). The narotic antagonist naloxone enhances clinical pain. *Nature*, **272**, 826–827.

LØKKEN, P. & SKJELBRED, P. (1980). Analgesic and anti-inflammatory effects of paracetamol evaluated by bilateral oral surgery. *Br. J. clin. Pharmac.*, **10**, 253S-260S.

PERT, A. (1980). Psychopharmacology of analgesia and pain. In *Pain, discomfort and humantarian care*, eds. Ng, L.K.Y. & Bonica, J.J., pp. 139–190. New York: Elsevier/North-Holland.

SKJELBRED, P. & LØKKEN, P. (1982a). Post-operative pain and inflammatory reaction reduced by injection of a corticosteroid. A controlled trial with bilateral oral surgery. *Eur. J. clin. Pharmac.*, **21**, 391–396.

SKJELBRED, P. & LØKKEN, P. (1982b). Reduction of pain and swelling by a corticosteroid injected 3 hours after surgery. *Eur. J. clin. Pharmac.*, **23**, 141–146.

SKJELBRED, P. & LØKKEN, P. (1982c). Codeine added to paracetamol induced adverse effects but did not increase analgesia. *Br. J. clin. Pharmac.*, **14**, 539–543.

SKRABANEK, P. (1978). Naloxone and placebo. *Lancet*, **ii**, 791.

(Received May 5, 1982, accepted September 29, 1982)