BACLOFEN PROLONGS THE ANALGESIC EFFECT OF FENTANYL IN MAN

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It has been shown that GABAergic compounds can potentiate opioid-induced analgesia (De Feudis, 1982) and that baclofen (β-(4-chlorophenyl)-γ-aminobutyric acid), possesses intrinsic analgesic activities in a variety of species (Levy and Proudfit, 1977). Thus, it seemed worthwhile to investigate the effects of baclofen in man during nitrous oxide—fentanyl anaesthesia in which fentanyl could be considered as the only variable affecting the control of pain.

PATIENTS AND METHODS

Three groups (10 patients each) undergoing transphenoidal hypophysectomy entered the study. The 30 patients (20 males), 25–60 years of age, and within 10% of their ideal body weight, were randomly assigned to one of the three groups. Mean (± SD) ages were 52 yr ± 6 for group 1, 46 yr ± 12 for group 2 and 46 yr ± 10 for group 3, and their mean weights were 70 kg ± 9, 67 kg ± 11 and 69 kg ± 10, respectively.

Patients in group 1 were pretreated with saline, those in group 2 with baclofen (Lioresal, Ciba-Geigy, Origgio, Italy) 0.6 mg kg⁻¹ i.m. in four doses for 5 days; and those in group 3 received baclofen 0.6 mg kg⁻¹ i.v. in 5% glucose 100 ml 45 min before the beginning of surgery. All the anaesthetics were conducted by the same anaesthetist (R.M.), who had participated in the planning of the trial, but was unaware of the specific test treatment received by the individual patient. Anaesthesia was maintained with 10% nitrous oxide in oxygen and analgesia was provided with subsequent administrations of fentanyl in single doses of 0.001 mg kg⁻¹. The intervals between the doses of fentanyl were variable and were used as a measure of the analgesic efficacy of the opioid. During surgery, several variables were monitored continuously: heart rate, arterial pressure, ECG, airway pressures, pupil size and evidence of lachrymation and sweating. Changes in these variables were used as criteria for the timing of the administrations of fentanyl. Fentanyl was administered when (there being no hypovolaemia) at least one of these variables, when observed at least 15 min after the previous dose of fentanyl, altered as follows: a 10% increase in heart rate, a 10% increase in arterial pressure, a 15% increase in airway pressure, or the appearance of lachrymation or sweating.

Blood samples were obtained before the induction of anaesthesia, at the beginning and the end of surgery, and on the first postoperative day to measure the plasma concentrations of the endogenous opioid β-endorphin. β-Endorphin concentration was measured by radioimmunoassay, as previously described, after separation by high pressure liquid chromatography (Panerai et al., 1983).

All patients were informed about the design of the study and gave their consent to the administration of baclofen and the blood sampling.

Statistical analysis of results was obtained by analysis of variance followed by Duncan test for multiple comparisons.

SUMMARY

Pretreatment with baclofen prolonged the duration of fentanyl-induced analgesia from 18 to 30 min in patients undergoing neurosurgical anaesthesia (fentanyl plus nitrous oxide in oxygen). This observation is consistent with a potentiating effect of GABA on opioid analgesia.

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*Fig. 1. Effect of pretreatment with saline (open column), baclofen i.m. (cross-hatched column) or baclofen i.v. (black column) on the time between the administrations of fentanyl. *P < 0.01 v. saline.

**TABLE I. β-Endorphin plasma concentrations (mean ± SEM)**

<table>
<thead>
<tr>
<th>Time</th>
<th>Concentration (fmol ml⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before surgery</td>
<td>30 ± 12</td>
</tr>
<tr>
<td>During surgery</td>
<td>50 ± 15</td>
</tr>
<tr>
<td>After surgery</td>
<td>36 ± 10</td>
</tr>
<tr>
<td>24 h after surgery</td>
<td>34 ± 12</td>
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</table>

**RESULTS**

Figure 1 shows the intervals of time between the individual doses of fentanyl. It shows that baclofen, administered either i.m. for 5 days, or i.v. immediately before the beginning of surgery, induced a significant increase in the mean time between the increments of fentanyl.

The data obtained also indicate that those patients receiving baclofen required less fentanyl. The amounts of fentanyl administered during the surgical procedure were significantly less (P < 0.001) in groups 2 (0.0070 mg kg⁻¹) and 3 (0.0063 mg kg⁻¹) than that required by the patients pretreated with saline (0.0101 mg kg⁻¹).

Table I shows that the β-endorphin plasma concentrations did not change significantly before, during or after surgery, and that they were similar in the three groups.

**DISCUSSION**

Our data are consistent with the data obtained in the experimental animal, suggesting that baclofen can potentiate opioid-induced analgesia.

At present we do not have a clear explanation for these results, although a few hypotheses can be put forward. We can exclude, in all probability, the involvement of β-endorphin in this effect of baclofen, although other endogenous opioids might be involved.

Baclofen can be thought of as acting through two different mechanisms. The most obvious action is through a GABAergic mechanism, since it has been shown that it can bind to GABA-B receptors (Bowery, 1982) and act as GABA agonist. Consistent with this observation, several GABAergic compounds have been shown to potentiate opioid-induced analgesia when administered peripherally (De Feudis, 1982). Moreover, GABA itself and other GABAergic compounds have been shown to elicit analgesia which is not reversible by naloxone (De Feudis, 1982). This observation is also consistent with our data, that seem to exclude a role for endogenous opioids in our particular study. Baclofen can also directly inhibit the effects of substance P-mediated neurotransmission (Saito, Konishi and Otsuka, 1975) and, therefore, inhibit the primary afferent neurones at the spinal level (Capek and Esplin, 1982).

Our results, although preliminary and obtained under specific conditions, offer interesting suggestions for the clinical use of the combination of baclofen and an opioid which will decrease the amounts of opioid required in anaesthesia and, possibly, in the treatment of chronic pain — if our results can be confirmed in an appropriate model.

**ACKNOWLEDGEMENT**

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**REFERENCES**