SITE OF ACTION OF FENTANYL IN INHIBITING THE PITUITARY-ADRENAL RESPONSE TO SURGERY IN MAN

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SUMMARY
To determine the site of action of fentanyl in attenuating the pituitary-adrenal response to surgery, we have measured serum concentrations of cortisol and growth hormone during and after a standardized surgical procedure in two groups of patients. One group received fentanyl 15 μg kg⁻¹ i.v. immediately before the start of surgery; a second group received fentanyl 15 μg kg⁻¹ i.v. together with corticotrophin releasing factor 100 μg i.v., growth hormone releasing hormone 100 μg i.v. and arginine vasopressin 10 units i.m. The concomitant administration of the releasing factors with the opioid resulted in a significantly greater serum concentration of cortisol 30, 60, 120 and 240 min after surgery commenced, compared with the group which received fentanyl alone. Similarly, the growth hormone response in the combined group was significantly greater than in the fentanyl-alone group 30 min after the start of surgery. We conclude that the inhibitory effect of fentanyl on surgically-induced secretion of pituitary hormone was mediated directly or indirectly via the hypothalamus.

KEY WORDS

Fentanyl is used commonly in anaesthetic practice. In high doses (> 50 μg kg⁻¹ i.v.), it prevents completely the pituitary hormonal response to pelvic and upper abdominal surgery [1]. We have shown that doses of fentanyl as small as 15 μg kg⁻¹ i.v. reduce the adrenocorticotropic hormone (ACTH), ß-endorphin, cortisol and growth hormone (GH) responses to pelvic surgery [2]. It is not known if these effects of fentanyl are mediated via the hypothalamus or the pituitary. In the present study, we have investigated the site of action of fentanyl 15 μg kg⁻¹ during surgery by the concomitant use of the hypothalamic releasing factors, growth hormone releasing hormone (GHRH), corticotrophin releasing factor (CRF) and arginine vasopressin (AVP).

METHODS AND RESULTS
We studied 12 healthy patients undergoing fallopian tubal surgery. They were not receiving any medication. The patients were allocated randomly to receive either fentanyl or fentanyl together with hypothalamic releasing factors. The study was approved by the Hospital Ethics Committee; the nature of the investigation was explained to the patients and written consent obtained.

All patients were premedicated orally with diazepam 10 mg 2 h before surgery. On arrival of the patient in the anaesthetic room, a central venous catheter was inserted percutaneously via an antecubital fossa vein for administration of drugs and fluids and collection of blood samples. After the patient had rested for 10 min, a control blood sample was obtained. Anaesthesia was induced in all patients with thiopentone 4–5 mg kg⁻¹, the trachea was intubated after administration of pancuronium 0.1 mg kg⁻¹, and the lungs ventilated with 70% nitrous oxide in oxygen. Fentanyl 15 μg kg⁻¹ i.v. was given to all patients just before surgery commenced. In those patients (n = 6) who received the hypothalamic releasing factors, human CRF 100 μg and GHRH 1–29 100 μg (Bachem Laboratories, Torrance, U.S.A.) were given i.v. and AVP 10 units (Pitressin, Parke-Davis, Eastleigh, Hants) was...
injected i.m. immediately after the fentanyl. The preparation of the CRF and GHRH for human injection was undertaken as described previously [3]. Sodium chloride solution 150 mmol litre\(^{-1}\) was administered i.v. at a rate of 6 ml kg\(^{-1}\) h\(^{-1}\) during the operation and 2 ml kg\(^{-1}\) h\(^{-1}\) after operation. Blood transfusion was not required, as measured blood loss did not exceed 220 ml.

Further venous blood samples were obtained at the start of surgery (0 min) and 30, 60, 120 and 240 min after surgery commenced. Arterial pressure and heart rate were measured at the same time as the blood samples were collected. Serum concentrations of cortisol and GH were measured by sensitive and specific radioimmunoassays [2]. All samples were analysed in a single assay; the intra-assay coefficients of variation were 6\% for cortisol and 8\% for GH.

The results are presented as mean values (SEM). Statistical evaluation of the data was undertaken using either two-way or one-way analysis of variance as appropriate.

There were no significant differences between the two groups of patients with respect to age, body weight and duration of surgery (34.3 (1.3) yr, 60.5 (4.3) kg and 81 (5) min, respectively, in the fentanyl-only group and 32.1 (1.6) yr, 58.3 (2.2) kg and 87 (4) min, respectively, in the releasing factors group).

Serum concentration of cortisol increased slowly in those patients who received fentanyl alone, from 222 nmol litre\(^{-1}\) at the start of surgery to a peak value of 492 nmol litre\(^{-1}\) after 120 min (\(P < 0.05\)) (fig. 1). In contrast, in the releasing factors group, cortisol increased significantly from 235 nmol litre\(^{-1}\) at the start of surgery to 562 nmol litre\(^{-1}\) after only 30 min (\(P < 0.01\)) and reached 736 nmol litre\(^{-1}\) after 120 min (\(P < 0.001\)). Serum concentrations of cortisol were significantly greater in the releasing factors group compared with the fentanyl-only group after 30, 60, 120 and 240 min (\(P < 0.01\)).

In the fentanyl-only group, serum GH increased from 4.8 mu. litre\(^{-1}\) at the start of surgery to 9.8 mu. litre\(^{-1}\) after 60 min, before declining to 5.9 mu. litre\(^{-1}\) after 240 min (fig. 1) (ns). The administration of releasing factors resulted in a massive increase in serum GH, from 6.3 mu. litre\(^{-1}\) at the start of surgery to 37.4 mu. litre\(^{-1}\) after only 30 min (\(P < 0.01\)) and 18.8 mu. litre\(^{-1}\) after 60 min (\(P < 0.05\)). Serum concentrations of GH were significantly greater in the releasing factors group compared with the fentanyl-only group after 30 min (\(P < 0.05\)).

**COMMENT**

The results show that the inhibitory effects of fentanyl 15 \(\mu\)g kg\(^{-1}\) on the pituitary-adrenal response to pelvic surgery may be overcome by the concomitant administration of CRF, GHRH and AVP. This indicates that the primary site of action of fentanyl during surgery is hypothalamic, either directly or indirectly, rather than pituitary.

Our findings are contrary to the conclusions drawn in a few previous studies examining the site of action of morphine in man [4, 5], in which it was concluded that morphine acted predominantly at the pituitary. It is important to note that both these studies examined the effects of morphine on basal and CRF-stimulated ACTH secretion in resting man. The present study is, we believe, the first to examine the site of action of an opioid given to inhibit stress-induced pituitary secretion in man. This important physiological difference, the stress of surgery compared with rest, may explain partly the discrepancy in the results. The dose of fentanyl used in this study, 15 \(\mu\)g kg\(^{-1}\), is approximately equivalent to morphine 1.5 mg kg\(^{-1}\). This equivalent dose of morphine is considerably greater than the 0.14 mg kg\(^{-1}\) s.c. used by Rittmaster and colleagues [5] and the 30 mg orally given by Allolio
and colleagues [4]. We cannot exclude the possibility that other doses of fentanyl may act at sites additional or alternative to the hypothalamus.

Nevertheless, our observation of a possible hypothalamic site of action of fentanyl is in keeping with other clinical data. It has been shown on many occasions that a given dose of opioid inhibits the secretion of several pituitary hormones simultaneously (ACTH, GH and AVP), in addition to suppressing sympathetic nervous system activity [1]. This strongly suggests a hypothalamic site, as the separate and distinct stimulatory and inhibitory mechanisms for each peptide militate against a single distal site of action.

We chose to administer AVP together with CRF and GHRH because it has been shown that the addition of AVP increases further the cortisol and GH responses to the hypothalamic factors [3]. The cortisol response found in patients who received fentanyl together with the releasing factors was almost identical to that obtained previously in patients undergoing the same surgery without an opioid [6]. It is tempting to infer that the cortisol changes observed in patients not receiving an opioid represented the maximal ACTH response, and that CRF and AVP were the major releasing factors involved in stimulating ACTH secretion during surgery. In contrast, the GH values found after GHRH and AVP were far greater than those noted without an opioid [6], indicating that the GH response to surgery did not represent maximal secretion.

In conclusion, fentanyl 15 μg kg⁻¹ attenuated the pituitary–adrenal hormonal response to surgery in man by an effect mediated via the hypothalamus.

REFERENCES