Naloxone in the treatment of anorexia nervosa: effect on weight gain and lipolysis[1]

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Summary: The effects of a constant intravenous infusion of naloxone in doses ranging from 3.2 to 6.4 mg/day were studied in a group of patients with anorexia nervosa. Patients showed a significantly greater weight gain during the infusion compared with the periods before and after naloxone. Plasma β-hydroxybutyrate and non-esterified fatty acid levels fell during the infusion. It is suggested that, in man, naloxone has an antilipolytic effect *in vivo*.

Introduction

In a previous communication from this department (Ghosh *et al.* 1977) we reported the effect of continuous intravenous infusions of naloxone in patients with diabetic ketoacidosis, and proposed an antilipolytic action for this drug. As a logical extension of these findings, we have investigated the effect of naloxone on weight gain and lipolysis in patients with anorexia nervosa.

Methods

Patients: Twelve patients with anorexia nervosa were studied whilst inpatients on a general medical ward. All subjects were female with a mean age of 22.5 years (range 16–38) and a mean weight of 37.6 kg, all patients being at least 25% below their ideal body weight. All gave informed consent to the study being carried out. The patients were treated with a reward and punishment regime supported by psychotherapy and were started on an antidepressant, usually amitriptyline, in doses ranging from 50–200 mg daily in divided doses from the day of admission. A dietary intake of 3000–4000 kcal was aimed for and all patients were weighed twice weekly.

Clinical protocol: At an average of 2.9 weeks after admission (range 1.5–6.5), the patients were started on a constant intravenous infusion of naloxone in doses ranging from 1.0 to 3.2 mg/12 hours, diluted to 20 ml with normal saline and delivered via a syringe fitted to a mechanical pump which the patients could carry around with them. The dose of naloxone was increased over the first week to a maximum of between 3.2 and 6.4 mg/day. The dose administered was somewhat arbitrary but was based on our previous experience in diabetic patients (Ghosh *et al.* 1977). The naloxone was administered for an average of 5 weeks (range 1–11 weeks), and on planned withdrawal of the drug the dose was gradually decreased over a period of at least 7 days. Unbeknown to the patients, two received only intravenous saline in the syringe pump for one week before or for one week after the naloxone infusion. Three patients had blood taken regularly before, during and after the naloxone infusion for estimation of plasma non-esterified fatty acid (NEFA) levels and β-hydroxybutyrate (β-OHB) as a measure of lipolysis and ketogenesis respectively.

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Laboratory methods: NEFAs were measured by the method of Dole & Meinertz (1960) and β-OHB by the method of Williamson *et al.* (1962). Normal range for NEFAs in our laboratory is 350–780 μmol/l and for β-OHB is 45–180 μmol/l.

Results

Figure 1 shows the mean weight gain per week of the 12 patients at various times in relation to the period of naloxone infusion. Patients gained significantly more weight in the week following the start of the naloxone infusion compared with the previous week and in the week prior to naloxone withdrawal compared with the following week. A greater weight gain was also seen during the entire period of naloxone infusion (mean 4.9 weeks) compared with the four weeks following withdrawal of the drug.

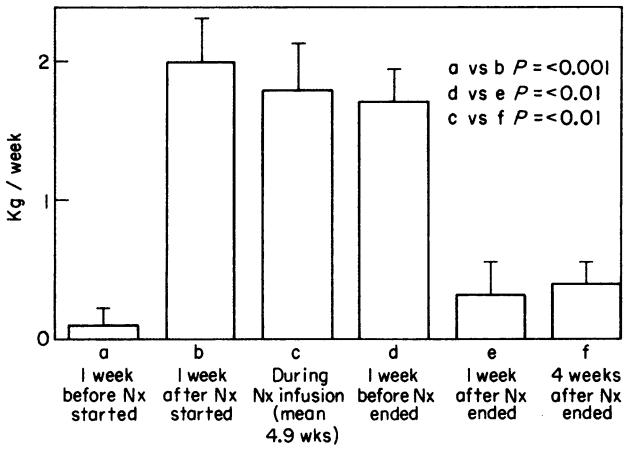

Figure 1. Weight gain before, during and after naloxone infusion in 12 patients with anorexia nervosa (mean ± s.e. (mean))

Figure 2 shows the changes in weight, and plasma β-OHB and NEFA levels in relation to the naloxone infusion periods in the three patients in whom these levels were measured. Patient 2 (Figure 2B) also received a saline infusion for twelve days prior to the naloxone. In the periods before and after the naloxone the NEFA and β-OHB levels were within the normal range in all three patients. In patients 1 (Figure 2A) and 2 (Figure 2B), there was a prompt fall in plasma β-OHB and NEFA levels to the subnormal range with a rise to pre-infusion levels within three days of withdrawal of naloxone. In patient 3 (Figure 2C), the fall was delayed and followed an initial rise in the levels of these compounds, but an equally prompt rise to pre-infusion levels occurred after naloxone was discontinued. In all three patients, weight gain was maximal during the naloxone infusion and the weight tended to level out or fall following the withdrawal of the drug.

Discussion

These findings would support our previous contention that constant infusions of naloxone over several days have an antilipolytic action, in that serum β-OHB and NEFA levels are suppressed and weight gain is promoted. At first sight, this would appear to be at variance with the report by Schwandt *et al.* (1979) who reported that the lipolytic action of porcine β-endorphin, which they demonstrated in rabbit adipocytes *in vitro,* was not inhibited by naloxone and could not be imitated by other opiate agonists. They concluded that this lipolytic effect could not be mediated via the opiate receptor.

In vivo, an alternative explanation is possible, in that the naloxone could act centrally to affect another control mechanism. Inhibition of lipolysis could be by inhibition of one of the many hormonal lipolytic mechanisms: this, however, is somewhat unlikely because of the absence of appropriate hormonal changes during naloxone infusion (R F Cook, I H Mills & R Moore, in preparation). Alteration of sympathetic control of lipolysis might be more probable.

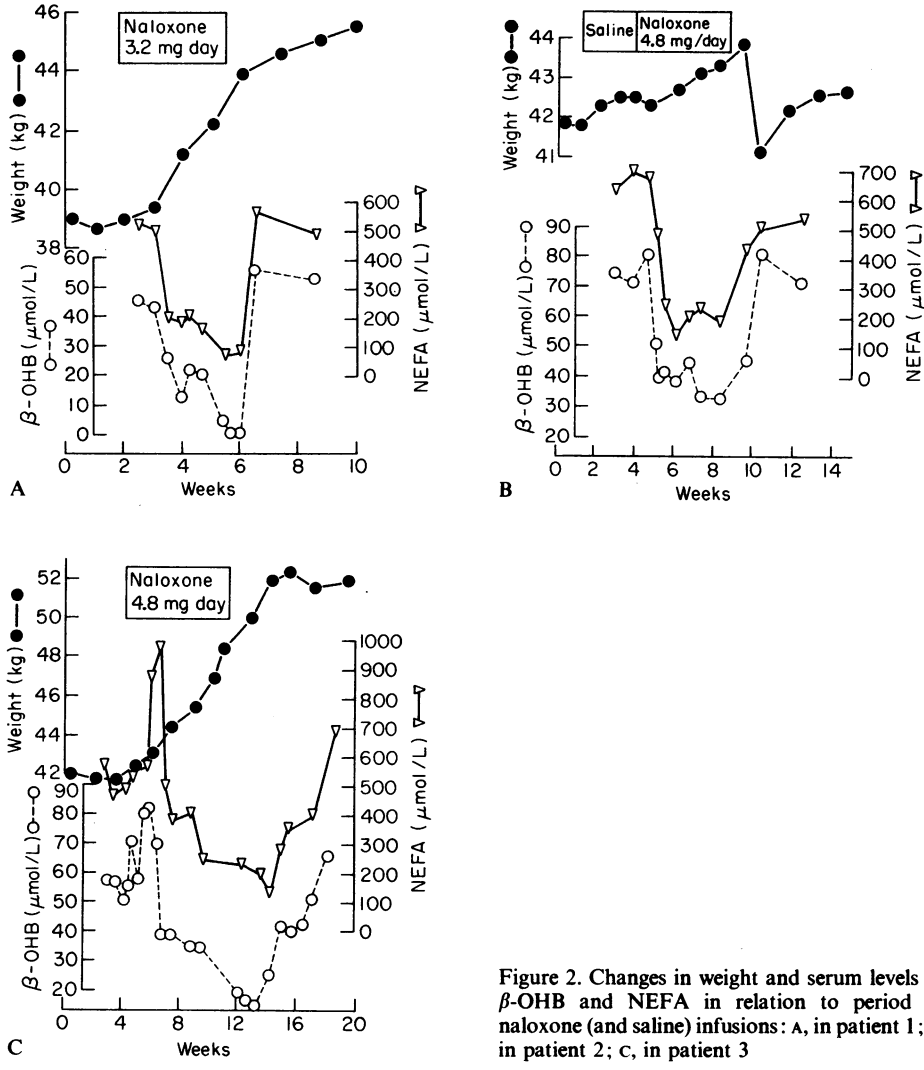

Figure 2. Changes in weight and serum levels of β-OHB and NEFA in relation to period of naloxone (and saline) infusions: A, in patient 1; B, in patient 2; C, in patient 3

The change in weight gain in the anorexic patients without a change in food consumption could be related to the fact that, without naloxone infusion, some anorexic patients increase their metabolic rate and may inhibit weight gain as a result. This particularly occurs in patients whose tri-iodothyronine levels rise into the hyperthyroid ranges (Moore & Mills 1979).

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