Intensive Care Med (1992) 18:362–363

Intensive Care Medicine


*Case reports*

# Reversal of neurological deficit with naloxone: an additional report

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Received: 3 December 1991; accepted: 25 May 1992

**Abstract.** We report the repeated improvement in neurological function following naloxone administration in a patient who developed acute hemiplegia after an intracranial neurological procedure. The mechanisms responsible for the neurological deficit and for its reversal by naloxone are discussed. A review of the literature suggests that the beneficial effect of naloxone can result from an improvement in haemodynamic status or from metabolic effects that could be favorable during cerebral ischaemia.

**Key words:** Naloxone – Neurological deficit – Post-operative complication

Over the past decade, endogenous opioids have been shown to have a role in the pathophysiology of circulatory shock, spinal trauma and cerebral ischaemia [1]. In addition, there is growing evidence that naloxone, an opiate antagonist, may have a beneficial effect in some ischaemic neurological deficits. We report a post-operative neurological deficit repeatedly reversed after naloxone administration and we discuss the hypothetical mechanisms of that beneficial effect.

## Case report

A 52-year-old, 70 kg, woman was admitted to our institution for the removal of a subarachnoid cyst in the right parieto-occipital region. Past medical history was significant for coronary artery disease treated with acebutolol (200 mg b.i.d.) and gastric ulceration treated with omeprazole (20 mg per day). She also had chronic left eye glaucoma occasionally treated with aceclidine chlorhydrate eyedrops. On admission, she complained of morning headache and left visual problems but neurological examination was normal. No cardiovascular symptoms were found and no carotid bruit was audible. Blood pressure was 140/80 mmHg and heart rate was 82 beats/min. Pre-anaesthetic medication consisted of acebutolol 200 mg and hydoxyzine 75 mg orally, midazolam 5 mg and atropine 0.5 mg intramuscularly, 2 h and 1 h respectively before surgery. Anaesthesia was induced intravenously with sufentanil (Sufenta) 20 μg and thiopental (Pentothal) 360 mg. Intubation was facilitated by atracurium (Tracrium) 40 mg. Anaesthesia was maintained with 0.4% isoflurane and 50% nitrous oxide in oxygen. Sufentanil was continuously infused at a decreasing rate from 35 μg to 10 μg/h. Additional doses of atracurium were given when necessary. ECG, arterial $O_2$ saturation ($SaO_2$) (Satlite, Datex), end tidal carbon dioxide ($ETCO_2$) and anaesthetic gas concentrations (Capnomac, Datex) were continuously monitored. Blood pressure was measured every 5 min (Dinamap, Critikon). Muscle relaxation was monitored with a peripheral nerve stimulator (Innervator, Fisher-Paykel). Arterial blood pressure remained stable at 90/50 mmHg and the patient was in sinus rhythm during the entire procedure. End tidal $CO_2$ was kept between 30 and 35 mmHg; $SaO_2$ remained between 98% and 100%. The intraoperative course was uneventful. Sufentanil was stopped 45 min before the end of surgery and isoflurane at the time of skin closure. Muscle paralysis was reversed with neostigmine 2.5 mg and atropine 1 mg. After full oxygenation, the patient was awake and alert. Blood pressure was 110/60 mmHg and pulse rate 72 beats/min. However, a complete left hemiplegia and a dilated, non reactive left pupil were noted. After extubation, the patient spontaneously recovered partial mobility of the left leg. She was then given 0.4 mg naloxone intravenously. Within a few seconds, the patient was able to move all extremities. However, careful neurological examination revealed a proximal monoparesis of the left upper limb and a persistent dilated left pupil. Blood pressure, pulse rate and respiratory rate were unchanged after naloxone administration. Computerized tomography (CT) showed only a moderate pneumocephalus in the right frontal area with no shift of the midline structures. Thereafter, the patient was admitted to the intensive care unit. Blood pressure was 120/80 mmHg. Blood count and serum electrolytes obtained at this time were in the normal range. A doppler examination did not reveal any abnormalities of the carotid systems. An ophthalmologist called in consultation diagnosed an acute left glaucoma crisis responsible for the dilated and non-reactive left pupil. Therapy was immediately started with aceclydine chlorhydrate eyedrops and intravenous acetazolamide. One hour after recovery, paralysis of the upper left limb reoccurred. A second bolus of 0.4 mg naloxone was injected intravenously and resulted in an immediate and spectacular improvement in neurological function, with no modification of mental status. Thereafter, a continuous naloxone infusion was initiated, at a rate of 0.4 mg/h.

Haemodynamic parameters remained stable overnight. The next morning, only a slight paresis of the proximal part of the upper left limb was observed; the perfusion of naloxone was stopped and the patient was discharged from the intensive care unit. The post-operative course was subsequently uneventful. The slight motor deficit resolved completely within one week. Hexamethyl-prolylenamineoxime Single Photon Emission Computer Tomography (HM-PAO SPECT) performed 10 days after surgery demonstrated decreased perfusion both in the left parieto-occipital and in the right frontal areas. A CT scan performed at the same time was normal. The patient left the hospital after 14 days with no neurological deficit.

## Discussion

Several reports of reversal of neurological deficit following administration of naloxone have appeared in the literature since the first two cases reported by Baskin and Hosobuchi in 1981 [2].

The mechanism responsible for the hemiplegia that occurred during recovery from an uneventful neurosurgical procedure is not clear. The first possibility is a neurological deficit of ischaemic origin: arterial hypotension could have induced some degree of cerebral ischaemia in a patient treated with a beta-blocking drug. In fact, beta-blocking drugs have little, if any, effect on cerebral blood flow. Arterial hypotension was moderate, transient and was not associated with hypovolemia. The patient was in sinus rhythm during the whole procedure. Naloxone administration changed neither blood pressure nor heart rate, suggesting that haemodynamics were unaffected by this drug. Therefore, an ischaemic origin is unlikely. The CT scan performed after surgery did not reveal any pathology that could have been treated surgically. Finally, the neurological deficit could be related to sufentanil administration. Indeed, the present observation is consistent with a recent report suggesting that sufentanil can worsen marginal neurological dysfunction [3]. Therefore, we cannot exclude a deleterious effect of sufentanil. However, in the present case, sufentanil was given at low doses, discontinued early and the patient was fully awake at the end of surgery.

Over the last few years, research focused on endogenous opioid peptides has emphasized their deleterious effects in shock and central nervous system injury [1]. There is growing evidence that naloxone can reverse ischaemic neurological deficits [2, 4, 5]. This action could be related to haemodynamic or metabolic effects.

The haemodynamic hypothesis is well documented. Opiate receptors have been identified at sites in the brain stem and hypothalamus, close to autonomic cardiovascular regulatory centers. Activation of these receptors by opioids during cerebral ischaemia is supposed to worsen cerebral damage by causing myocardial depression and by decreasing cardiac output [6]. Naloxone has been shown to improve haemodynamic status in pathological situations [6] and to increase CBF even in stable haemodynamic conditions. This haemodynamic hypothesis has not received general agreement. Indeed, improvement in neurological function after naloxone has been reported with stable blood pressure and unchanged CBF [2, 7]. On the other hand, some studies could not demonstrate any effect of naloxone on cerebral or systemic haemodynamic parameters [8].

The metabolic effects of naloxone were recently summarized by Skarphedinsson [7]. They include inhibition of proteolysis, stabilization of lysosomal membranes, inhibition of lipid peroxidation, modulation of cyclic adenosine monophosphate, transmembrane calcium fluxes and platelet aggregation, and antagonism of excitatory aminoacids. Most of these effects could be beneficial during cerebral ischaemia. Experimental data have also demonstrated a tonic inhibitory action of endogenous opioids on afferent sensory pathways, suggesting that naloxone can reverse an endorphinergic depression of viable neuronal function but does not affect cell survival [7].

Although the role of endogenous opioids in cerebral ischaemia is still poorly understood, there is clear evidence that naloxone can improve some ischaemic neurological deficits when given early after the onset of ischaemia [9]. There is no proof that naloxone has any effect on outcome and that patients would not have recovered normal neurological function without naloxone. If neurological improvement is only transient, naloxone administration could be used as a predictive test: naloxone would transiently reverse a neurological deficit only in patients who will recover normal neurological function [9]. Whether outcome in such patients is really improved by naloxone remains to be answered by prospective trials. Finally, naloxone should be used carefully because of potential cardiovascular effects such as uncontrolled hypertension and arrhythmias [10].

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