Anaphylaxis precipitated by intravenous morphine sulphate

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Abstract
Morphine is a potent opioid that is used as one of the standard drugs for pain management in perioperative practice. It was first synthesised in 1952 and is the drug against which all other analgesic drugs are compared. It is also one of the most abused drugs worldwide. We present an interesting case of anaphylaxis that was precipitated by a morphine bolus and required aggressive resuscitation. The episode was temporally related to injection and confirmed biochemically by a raised tryptase result.

Case Report

Our patient was a 56 year old man who presented with increasing lower back pain post anterior-posterior fusion. He had developed right leg neuropathy and radiculopathy due to spinal stenosis. He had had three previous spinal surgeries;the most recent in 1996 . for a S1-L4 fusion. He had experienced no problem with general anaesthesia. His only significant medical problem was hypertension but this was well controlled with Norvasc. He was still physically active and did approximately 12 hours of exercise a week which included spinning classes and weight training. He was sensitive to celebrex, which precipitated a rash but had no other known drug allergies. Planned surgery was a revision and extension of fusion. Starting hematocrit was 39.

He was premedicated with midazolam 2 mg iv and anesthesia was induced with fentanyl 250 mg , propofol 200 mg and rocuronium 50 mg . Once anesthesia was induced a 20 G arterial line was inserted into the radial artery and a triple lumen central line was inserted into the right internal jugular vein on the second pass. Pressure was held on the carotid artery which was punctured by the seeker needle. No complications arose. Initial cvp reading was 14 cm H2O. He was cardiovascularly stable. 1 g of kefsol was given over 2 minutes following a test dose. Maintenance of anesthesia was with remifentanil infusion at 0.1 mg/kg/min and desflurane 2% with nitrous oxide. Fluid was replaced with a combination of crystalloid and albumin. His estimated blood loss was 2500 ml and at 5 and a half hours he was transfused 1 unit of autologous blood.

At six and a half hours into the surgery the remifentanil infusion was stopped as the surgeons commenced closing the wound and the patient was given a 10 mg bolus of morphine sulphate in anticipation of managing his analgesia requirements. At this time his blood pressure was 110/60 and his heart rate was 75 bpm consistent with what it had been throughout the surgery. He started spontaneous respiration on 1.0 FiO_2 . 10 minutes after the morphine bolus was administered he became tachycardic to 110 bpm , his blood pressure (arterial reading) was 60/ 28 ; noninvasive was undetectable , and CVP was 4cm H_2O. He had palpable radial pulses and pneumothorax was excluded by bilateral breath sounds.

The blood pressure was refractory to volume replacement with colloid, crystalloid and 500cc of cell saved blood and the use of pressors: 50 mg of ephedrine and 1mg neosynephrine. His blood pressure was approximately 80/44 and HR =110/min. He continued to be refractory for 15 minutes at which time we gave him a bolus of 300 mg of epinephrine which stabilised his blood pressure at 100/50 but he remained tachycardic. He was turned supine and noted to be flushed and warm and moving his limbs. He was extubated awake and transported to the recovery unit, breathing oxygen via a Jackson-Rees circuit but still requiring epinephrine boluses to maintain his pressure at 100 systolic. In the recovery unit his haemodynamic status had improved with the epinephrine boluses and it was decided not to start an epinephrine infusion. This had taken 45 minutes to resolve. We sent a tryptase test , blood count, coagulation screen and electrolytes.

He stabilised after an aggressive resuscitation in which he received 4l of crystalloid, 3l of albumen and 1l of blood and pressor support. His analgesic requirements were controlled by a hydroxymorphone PCA and he was discharged to the ward with no further problems.

His tryptase results were significant for anaphylactoid response which we surmise was precipitated by the morphine sulphate bolus. His beta tryptase was 14ng/ml (ref. range: <1 ng/ml) and unicap total tryptase: 63 ng/ml (ref. range : 1 – 10 ng/ml).

DISCUSSION

The case that we present is that of a 56 year old man who underwent a multilevel spinal fusion and developed severe and prolonged anaphylaxis that required aggressive resuscitation. The anaphylaxis was temporally precipitated by morphine sulphate injection and this was confirmed biochemically by a tryptase result that was very significantly raised.

Morphine is used for premedication but more commonly for its potent analgesic qualities to great effect in our perioperative practice. Peak effect occurs at 15-20 minutes after iv administration, action lasts 4-5 hours. It is hepatically metabolised to morphine 3- and 6-glucuronide, the latter of which is active. It has minimal effects on the CVS. The predominant effect is orthostatic hypotension secondary to a decrease in peripheral vascular resistance probably due to histamine release. Hypotension has also been reported with use

which is thought to be due to a central effect.

It is well known to act on the vagus nerve leading to occasional bradycardia. Morphine does precipitate histamine release which may cause vasodilatasion, bronchoconstriction, itching (nasal), flushing. [Sasada and smith]

Of the drugs used in anesthesia those implicated in immediate allergic reaction are relatively small in number and include neuromuscular blocking agents, β- lactam antibiotics and rarely narcotics. [baldo] . Severe anaphylaxis has seldom been reported other then in literature documenting drug overdose in heroin addicts. [edston]. Our case clearly presented as anaphylaxis showing hypotension (80% present with this symptom) , flushing and a distinct temporal relationship to morphine injection.

Acute anaphylaxis is mediated by histamine release from mast cells and basophils but this has a very short half life and requires sampling within approximately 10 minutes[fisher]. Tryptase which is also released from mast cell degranulation remains raise for 1-6 hours and thus, is a better marker. It is a specialised test and ours was performed at the Virginia Commonwealth University where the unicap total tryptase was 63 ng/ml (ref. range 1-10 ng/ml). This test is benefit of having performed a tryptase test as part of our follow up is to establish a definite diagnosis of anaphylaxis which this result confirms.

What we are drawing attention to is the fact that anaphylaxis can be precipitated by morphine and that this has only been suggested previously in studies of heroin addicts who have "overdosed". Edston et al measured the tryptase in post mortem blood of 22 heroin addicts dying suddenly after injection of morphine. In 32% the concentration was elevated and the mean value was significantly elevated compared to a control group who had died from known causes. This indicates that death was preceded by mast cell degranulation. The levels of morphine in the blood were all below 0.2 mg/ml less then that needed to cause overdose. The unspecific liberation of histamine and other mast cell constituents would be the most likely explanation of this observation. The results of this elegant study support the contention that many heroin fatalities are probably anaphylactoid in origin rather then due to overdose.

Following on our experience which corroborates the findings of Edston et alwe would like to draw attention to the potential severe anaphylactic reaction that morphine can precipitate. This patient had three previous surgeries in which he was treated with morphine. It is likely that at this time the patient was sensitized to morphine.

If one suspects anaphylaxis resusitation needs to be prompt and aggressive utilising fluid and pressors. We suggest a low threshold for using epinephrine early on in the resuscitaion. Awareness of the potential severity is paramount. It is always important to exclude other differential diagnoses and to be aware that they can still be underlying, for example myocardial infarction, pulmonary embolus, pneumothorax or hypovolaemia.

The treatment of acute anaphylaxis does not end with the acute episode. The cause of the reaction should be determined where possible. This requires cutaneous testing and radioimmunoassays for specific IgE. We would suggest follow up allergy testing and counseling of the patient. Unfortunately, this patient was lost to follow up. We also suggest that patients who are diagnosed with anaphylaxis should wear a med alert bracelet.

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