Severe Neutropenia After Intermittant Use of Nitrous Oxide in Pregnancy: Not a laughing matter

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Citation

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Abstract

Although nitrous oxide is commonly used in labour for analgesia, it is not an innocuous agent. Adverse haematologic, neurologic, immune and reproductive effects have been identified with prolonged exposure to nitrous oxide. We present a unique case report of severe neutropenia following intermittent use of Entonox during pregnancy which resolved spontaneously following stoppage of its use. The present generation cannot become complacent with its use and this case report is a reminder that exposure to analgesic concentrations of nitrous oxide should not be prolonged.

INTRODUCTION

A mixture of nitrous oxide and oxygen in equal proportions (Entonox or Equanox) is an effective analgesic and is considered safe with minimal side effects. The mixture is ideal for treating short term pain and is extensively used in labour. We report a serious haematological problem in a pregnant patient using such a mixture for analgesia.

CASE REPORT

A 23 year old, Para 1 with a previous term normal vaginal delivery, presented with abdominal pain at 32 weeks of pregnancy. She booked at seven weeks of pregnancy and had several admissions for vague symptoms in this pregnancy. In her past, she was treated for bulimia and depression and had several social problems.

On examination, she was distressed with pain, and an abdominal examination showed tightenings but with no changes in the cervix. With an impression of threatened preterm labour, she was given steroids and tocolytics but this did not help with the pain. She refused pethidine and other analgesics and was using Entonox for pain relief.

Extensive investigations were done to find out the cause for her abdominal pain. Urine dipstick did not reveal any evidence of infection. All blood investigations including serum amylase were within normal limits. Blood culture and urine culture showed no growth. Abdominal ultrasound and ultrasound of the kidneys, ureters and bladder was within normal limits. Ultrasound of the fetus was also normal. Pain relief was a problem for her since no cause for her abdominal pain could be found. She was insistent on being delivered, which was discouraged in view of the prematurity of the baby. She was constantly reviewed by the anaesthetic team with regards to her pain relief. She was warned about the risks of bone marrow suppression with prolonged use of Entonox but she refused all other forms of analgesia offered to her like paracetamol, codydramol, pethidine, morphine, temazepam, and continued to use Entonox for the next 10 days.

She developed several painful mouth ulcers and so could not use the Entonox. A routine full blood count showed marked neutropenia with a WBC count of 2.1×10*9/L, a neutrophil count of 0.6×10*9/L, lymphocyte count of 1.4×10*9/L and monocyte count of 0.1×10*9/L. The blood film showed no blast cells.

Suspecting toxicity due to Entonox, no further Entonox was given to the patient. On consulting with the Haematologist, full blood count was done daily, with a plan for a bone marrow biopsy if the neutrophil count continued to fall. Fortunately, further full blood counts showed the neutrophil count to be rising. In four days time, the full blood count came back to normal and the patient was discharged home. Further full blood counts were within normal limits and she had no further admissions. She was induced at 38 weeks of pregnancy and had a normal vaginal delivery.

DISCUSSION

Nitrous oxide is an effective analgesic in sub-anaesthetic concentrations. It has a special advantage of a very rapid

onset of analgesia. But the duration of use as an analgesic is limited by its effect on bone marrow.[1]

Entonox should not be used for more that 24 hours without monitoring of the peripheral blood for features of megalablastic anemia and leukopenia. As a precaution, use of Entonox for more than 4 days, should be accompanied by full blood counts to monitor for leucocyte counts and for evidence of megaloblastic changes in red blood cells.[1] The Overdose Exposure Standard (OES) for Entonox (8 hour Time-weighted average TWA) is 100 ppm.[2] Thorough ventilation and scavenging of waste gases which reduces the level of Entonox to <100ppm is routine in operating theatres but not in the delivery suite.[3]

Neutropenia following prolonged inhalation of nitrous oxide is caused by a different mechanism to megaloblastic anemia. The cobalt in vitamin B12 is oxidised to the trivalent form by chemical reaction with nitrous oxide. B12 is thereby inactivated and this interferes with folate metabolism and thymidine synthesis. The effect may be detected after only a few hours in vivo exposure of mammals to 50% nitrous oxide.

It reduces not only production but also motility and chemotactic response of leucocytes.[4] Retrospective surveys of dental and medical personnel have linked occupational exposure to N2O with a number of health problems and reproductive derangements.[5] A number of epidemiological studies have linked occupational exposure to nitrous oxide with spontaneous abortions, congenital abnormality, and reduced rates of fertility, including reported effects in midwives.[6] But not many studies have been undertaken to study the haematological toxicity of Entonox in labouring women and importantly health care attendants taking care of these women.

Prolonged use of Entonox for pain relief in this case i.e. 10 days, is much longer than what it is intended to be used for. Also nowadays, awareness of the dangers of prolonged exposure of nitrous oxide is increased and the risk is avoided. But our patient continued to use Entonox in spite of being warned of its adverse effects on the bone marrow.

From the fact that this case occurred strongly suggests that the present generation cannot become complacent and still needs to be reminded that exposure to analgesic concentrations of nitrous oxide should not be prolonged. Long term exposure to high concentrations of Entonox i.e. months has been known to produce neurological symptoms due to sub-acute degeneration of spinal cord but neutropenia has not been reported yet. [7]

This case report highlights one of the potential dangers of long term intermittent use of Entonox in pregnant women. It is advisable to limit the use of Entonox only during labour and only for short durations. Long term use of Entonox should be discouraged, and if used, needs close monitoring of full blood counts to limit its sideffects.

It is unlikely that this adverse effect will be present with the more conventional shorter duration of Entonox usage. More studies needs to be done on the effects of long term exposure to Entonox in delivery suite personnel and similarly methods of controlling nitrous oxide concentrations to approximate the recommended levels in the labour room environment should be looked into.

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