MEGALOBLASTIC BONE MARROW CHANGES AFTER REPEATED NITROUS OXIDE ANAESTHESIA
Reversal with Folinic Acid

J. F. NUNN, I. CHANARIN, A. G. TANNER AND E. R. T. C. OWEN

An 18-year-old male Sikh, who took a meat diet and was previously in normal health, sustained a deep penetrating stab wound in his left hypochondrium shortly before midnight as part of a stabbing affray in our District. At laparotomy by A.T. (2.15 a.m.), he was found to have a haemoperitoneum of 6 litre as a result of a divided mesenteric artery and a splenic capsular tear; there were also six perforations of the first loop of jejunum. A small bowel resection and splenectomy were performed. The anaesthetic included 70% nitrous oxide and lasted for 105 min. During the operation he received a total of 31 units of blood, 5 litre of Haemaccel, together with fresh frozen plasma and platelets. There were technical difficulties in the measurement of arterial pressure, but he had no palpable pulse for at least 30 min. He was returned to the Intensive Therapy Unit. His circulatory state remained unstable and because of persistent intra-abdominal bleeding it was decided to undertake a further laparotomy at 11.00 a.m. on the same day.

Amos and colleagues (1982) have reported an 89% mortality in 18 patients admitted to an intensive therapy unit with megaloblastic bone marrow changes following the administration of nitrous oxide. An abnormal deoxyuridine suppression (dU) test was observed in 11 of 13 patients who had received nitrous oxide for 2 h or less, and one of these patients was megaloblastic. Our patient had already received nitrous oxide for 105 min and a second administration could only aggravate inactivation of vitamin B₁₂. Nevertheless, nitrous oxide was an attractive choice of anaesthetic for a patient already paralysed and ventilated, but in an unstable circulatory state. It was considered that the patient’s condition justified marrow puncture and this was carried out as soon as the second anaesthetic was induced.

Anaesthesia was induced by J.N. with nitrous oxide in oxygen at 11.15 a.m.; folinic acid 30 mg i.v. was given and anaesthesia continued for a total of 2 h. At the second laparotomy (E. O.), a further 5–6 litre of blood was found in the peritoneal cavity as a result of bleeding from the short gastric vessels. Bleeding points were secured and the abdomen closed. A second marrow puncture was undertaken 4 h after the second anaesthetic.

Recovery was uneventful and the trachea was extubated at midnight. Following surgery, the patient received folinic acid 30 mg daily for 5 days, during which his leucocyte count increased from 9.1 to 29.5 x 10³ mm⁻³. He left hospital 9 days after the second operation.

**SUMMARY**
A seriously ill patient was found to have megaloblastic changes in his bone marrow after a nitrous oxide anaesthesia which lasted for 105 min. After an interval of 7 h a second nitrous oxide anaesthetic was administered, during which the patient received 30 mg of folinic acid. His marrow was normal when assessed 4 h later.
Second bone marrow (5.30 p.m.)

This showed a restoration of normoblastic haemopoiesis and return to a normal dU suppression test (9.4%).

COMMENT

In the dU suppression test, marrow cells are incubated with deoxyuridine and the capacity of the marrow to methylate this to thymidine is assessed. The essential carbon donor is 5,10-methylene tetrahydrofolate, the concentration of which depends on normally functioning vitamin B$_{12}$ and folate (Nunn and Chanarin, 1985). Normal marrow will meet more than 90% of its thymidine requirement by methylating uridine and, when $^3$H-thymidine is added, less than 10% of the preformed thymidine is used. In contrast, when there is impaired thymidine synthesis in megaloblastic bone marrow, including that becoming megaloblastic as a result of nitrous oxide exposure, more than 10% of preformed $^3$H-thymidine is incorporated.

The megaloblastic appearance of the marrow and the abnormal dU suppression test at the time of the second laparotomy leave little doubt that there was impaired methionine synthase activity as a result of oxidation of its co-factor, vitamin B$_{12}$, by the nitrous oxide. A second exposure to nitrous oxide would have made this worse, since inhibition of methionine synthase is rapid but recovery is slow (Deacon et al., 1980). However, the administration of folinic acid, a precursor of 5,10-methylene tetrahydrofolate, resulted in a normal marrow and dU suppression test a few hours after the second administration of nitrous oxide. Direct demonstration of inactivation of vitamin B$_{12}$ would have required liver biopsy, which was not considered justifiable.

This patient provides confirmation of the observation by Amos and colleagues (1982) that administrations of nitrous oxide lasting for 2 h or less may result in impaired thymidine synthesis and megaloblastic bone marrow changes in seriously ill patients. In contrast, no changes were observed in relatively healthy patients receiving nitrous oxide for up to 6 h (O'Sullivan et al., 1981). We also confirm that folinic acid in appropriate dosage can offset the effect of nitrous oxide, with rapid restoration of a normal marrow. It has been found to be effective following exposure to nitrous oxide lasting 24 h (O'Sullivan et al., 1981; Skacel et al., 1982; Amos et al., 1984; Kano et al., 1984). This case illustrates the potential value of folinic acid for seriously ill patients who receive nitrous oxide repeated after a short interval.

ACKNOWLEDGEMENT

We are indebted to Mr A. G. Cox, F.R.C.S., for permission to report a patient admitted under his care.

REFERENCES


