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Failure to Correct Nitrous Oxide Toxicity with Folinic Acid

To the Editor:—Prolonged administration of N_2O produces severe marrow depression. This is due to the effect of N_2O which inactivates vitamin B_{12} and leads to severe megaloblastosis, the synthesis of DNA, as measured in the deoxyuridine (dU) suppression test, becoming abnormal. O'Sullivan *et al.*[1] recently have reported prevention of abnormal dU suppression tests and megaloblastic hemopoiesis following the use of N_2O, by prior administration of folinic acid. This is contrary to our own experience in both humans and the rat.

At the time of writing, we have studied three patients receiving 4.5, 7, and 24 h of 70% N_2O. dU suppression tests were performed by the method of Metz *et al.*[2] with the modification of Ganeshaguru and Hoffbrand.[3] All had normal preoperative dU values of 2.9 ± 1.0% (mean ± SD). Less than 10% generally is accepted as a normal result.[3–5] The use of N_2O produced a rise in dU suppression in all three patients to values of 12.8%, 20.3%, and 21.4%, respectively, despite high doses of folinic acid (table 1), which were administered orally in the second patient (in the same manner as described by O'Sullivan *et al.*) and intravenously in the other two. The patient receiving N_2O for 24 h developed megaloblastic hemopoiesis, despite folinic acid.

It is not clear how the dU suppression tests were performed by O'Sullivan *et al.*, and, in particular, whether the autologous serum used in the incubation of marrow cells was that taken concurrently with the marrow or obtained prior to folate administration. Serum containing high levels of folate may cause spurious *in vitro* alteration of dU suppression. We raise this point because, in one patient after 24 h N_2O (without oral folinic), there was a fall in dU suppression value, and the expected reduction in the dU value in normoblastic marrows when folinic is added, was not observed. An abnormal result (12%) in a "control" patient became more abnormal (14%), although he had not received N_2O. These results differ from other published data.[3,6,7]

It would be unwise for anesthetists to assume on the basis of the report of O'Sullivan *et al.* that the toxicity of prolonged N_2O is overcome by these doses of folinic acid, because this has not been our experience.

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ADDENDUM

More recently, we have completely prevented these toxic effects of N_2O with 30 mg folinic acid, iv, every 5 hours throughout a 24-h period of exposure. The dU suppression result was 3.0% before N_2O and 3.2% after 24 hours without any marrow changes. These confirm the data reported by Nanciekievill and his colleagues at the European Congress of Anaesthèsiology in London, September 1982.

TABLE 1. Data of Three Patients Receiving N_2O with Folinic Acid

Patient	Duration of N_2O (h)	Folinic Acid Administration	Serum Folate (ng/ml)		dU Suppression (%)	
			Preoperative	Postoperative	Preoperative	Postoperative
1	4.5	27 mg, iv	6.8	355	1.6	12.8
2	7	42 mg, po*	4.6	94	3.4	20.3
3	24	42 mg, iv	7.5	150	3.8	21.4

* Regime used by O'Sullivan *et al.*