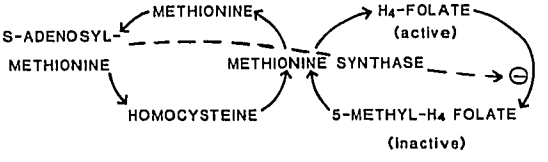
DOES NITROUS OXIDE INACTIVATION OF METHIONINE SYNTHASE DECREASE FOLIC ACID ACTIVITY IN MAN?

R.A. Hawkins, Ph.D., M.T. Snider, M.D., Ph.D., G.B. Russell, M.D., D.W. Davis, Ph.D., J.F. Biebuyck, M.B., Ch.B, D. Phil., Departments of Anesthesia and Physiology, The Pennsylvania State University College of Medicine, The Milton S. Hershey Medical Center, Hershey, Pennsylvania 17033

Prolonged exposure to N_2O can cause certain undesirable effects in humans and experimental animals including megaloblastic bone marrow changes and neurological changes that mimic vitamin B_{12} deficiency. The biochemical basis for these effects seem to be closely related to the loss of methionine synthase activity (1). Methionine synthase is a key link between two important cycles; one cycle is involved in the synthesis of S-adenosyl-methionine, an important intermediary metabolite in methylation reactions and the other cycle involves folic acid. Inactivation of methionine synthase can, in principle, bring both of these cycles to a halt if tissue methionine concentrations are not maintained (2,3). This could lead to a decreased rate of methylation and to trapping of folate as the biologically inactive methyl derivative thereby causing a functional folate deficiency with impairment of folate-dependent reactions. Although it is known that N_2O can inactivate methionine synthase activity in a matter of hours the question is open whether this has important consequences for patients exposed to routine anesthetic procedures. The focus of our study was to evaluate whether there was a detectable reduction in one of the folate-dependent reactions; the oxidation of histidine.



Methods: In order to study the effects of N_2O alone it is desirable to eliminate other drugs and anesthetics. But, this is difficult because at normal atmospheric pressures even 70% N_2O is not sufficient to induce and maintain anesthesia. One solution is to raise the ambient pressure to 2 atm. Under these circumstances the N_2O partial pressure can be adjusted to a level sufficient to produce anesthesia and maintain the partial pressure of oxygen at a safe level. The advantage of this protocol is that N_2O can be studied in the absence of other confounding variables. After the appropriate institutional permission and volunteer informed consent were obtained, six human volunteers were anesthetized in an hyperbaric chamber at 2 atm pressures with N_2O and oxygen. All volunteers were ASA I males aged 20-34 years who had been fasted overnight. After the chamber pressure was increased to 2 atm, each volunteer underwent an inhalation induction with 1.5 atm N_2O. Anesthesia was established and intravenous succinylcholine was given to five of the subjects who were then intubated. One patient was maintained by mask. Folic acid deficiency was tested by histidine loading. In the absence of folic acid the degradation of histidine stops at formiminoglutamate (FIGLU) which accumulates in the urine. The subjects were given an histidine load for each of two 24 h periods before N_2O exposure and for several days thereafter. Urine was collected every 8 h. Urinary FIGLU was converted to glutamate which was assayed enzymatically.

Results: The range of N_2O exposure was from 2.2 to 4.9 atm.hour. This corresponds to the delivery of 70% N_2O for 3.1 to 7.0 hours and covers the range of most surgical operations. Methionine synthase is decreased by about 40% per atm.hour of exposure (4). Thus from 60 to >90% of methionine synthase should have been inactivated. Two subjects (1 and 3) showed increased FIGLU excretion for several days after exposure. The remaining four subjects showed no indication of folate deficiency.

Discussion: N_2O has been used as an anesthetic for many years; only recently has it come under closer scrutiny because of its ability to inactivate methionine synthase. Our experiments were designed to evaluate one of the predicted biochemical consequences. It may be predicted that inactivation of methionine synthase would lead to a fall in tissue methionine and S-adenosylmethionine concentrations. This in turn could promote the synthesis of methyltetrahydrofolate, a form which is inactive in many biochemical reactions including the oxidation of histidine. We found no sign of a functional deficiency in four subjects but signs of a mild and persistent deficiency (over a period of several days) in two. Although further experiments need to be done in order to settle the issue conclusively, it would appear from these results that N_2O may not disrupt human biochemistry to the extent predicted from animal experiments.

References

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FORMIMINOGLUTAMATE EXCRETION AFTER N_2O ANESTHESIA

Subject	Exposure atm.hours	Day 1	Day 2	Day 3	Day 4	Day 5
		% of Baseline				
1	2.2	208	262	169	---	---
2	3.5	114	79	136	86	86
3	4.7	--	181	185	204	189
4	4.4	82	155	82	82	68
5	4.7	114	102	102	71	95
6	4.9	56	69	92	54	88