METHOTREXATE THERAPY AND NITROUS OXIDE ANESTHESIA

To the Editor: Treatment of cancers in childhood often involves a short intravenous infusion of high-dose methotrexate (>30 mg per kilogram of body weight) followed by "rescue" therapy with leucovorin (5-formyl-tetrahydrofolate). Concurrent intraspinal infusion of methotrexate may also be used.[1] This treatment may be performed during general anesthesia. Nitrous oxide anesthesia is often used in pediatric oncology units. There is, however, evidence that the drug combination of nitrous oxide and methotrexate may be hazardous.

Methotrexate acts by inhibiting the enzyme dihydrofolate reductase and thereby blocks the regeneration of tetrahydrofolate from dihydrofolate.[2] This results in the inhibition of several processes dependent on reduced folates, including the conversion of homocysteine to methionine.[3] In most tissues this reaction is catalyzed by the cobalamin-dependent enzyme 5-methyltetrahydrofolate-homocysteine methyltransferase (EC 2.1.1.13.). Conversely, homocysteine serves as a methyl acceptor in this reaction and is probably required for the conversion of 5-methyltetrahydrofolate to tetrahydrofolate.[4] We have recently provided evidence suggesting that these mechanisms may operate in both intact cells and patients, by demonstrating an increased homocysteine release into the medium of cultured cells and into the urine and plasma of patients after methotrexate exposure.[4]

The mechanism of the leucovorin rescue has been the subject of much debate. The finding that 5-formyltetrahydrofolate is converted to 5-methyltetrahydrofolate in cultured cells[5] suggests that the rescue effect depends on the further metabolism of 5-methyltetrahydrofolate to form tetrahydrofolate, catalyzed by 5-methyltetrahydrofolate-homocysteine methyltransferase. Theoretically, the rescue effect therefore depends on the activity of this enzyme and on the presence of homocysteine.

The anesthetic agent nitrous oxide, once considered chemically inert and devoid of side effects, was shown in 1968 to oxidize vitamin B_{12} irreversibly, and thereby to inhibit 5-methyltetrahydrofolate-homocysteine methyltransferase.[6] In fact, nitrous oxide has been used as an experimental tool to evaluate the role of this enzyme in the rescue effect of 5-methyltetrahydrofolate and 5-formyltetrahydrofolate in methotrexate-challenged lymphoblasts, and has been shown to reduce the rescue effect of the former compound.[7] In humans, nitrous oxide reduces the methionine content in plasma,[6] which is in accordance with the inhibition of cobalamin-dependent methionine synthesis from homocysteine.

Although the rescue therapy seems to work in children exposed to nitrous oxide, it is conceivable that nitrous oxide may reduce the therapeutic benefit and increase the side effects of methotrexate therapy. Until these possibilities have been rejected, nitrous oxide should be used with caution in patients receiving methotrexate.

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