Title : HALOTHANE IMMUNOSUPPRESSION IN TUMOR-BEARING MICE

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Introduction. Anesthetic agents may compromise many aspects of host immune responsiveness that include depression of antibody synthesis, bone marrow, phagocytosis, and macrophage migration, and diminished resistance to infection and the development of neoplasia.[1,2] The present investigation was designed to demonstrate whether the depression of cell-mediated immunity in tumor-bearing hosts is potentiated by the induction of anesthesia with halothane

Methods. Seventy-five inbred C3Hf/He male mice, 10-14 weeks of age, were used. The tumor was a transplantable fibrosarcoma indigenous to the C3Hf/He strain of mice and is presently in the 438th transplant generation. Both the in vivo and in vitro effects of halothane anesthesia on splenic lymphocytes were examined. Normal and tumor-bearing mice were either anesthetized by exposure to 1.5% halothane, as monitored by the gas chromatograph, for 1.5 hours (experimental) or were exposed to O_2 (Control 1) or to air (Control 2) under corresponsing conditions. Mice were killed by cervical dislocation upon recovery from the anesthetic agent. Their spleens were removed aseptically and a single cell suspension prepared in Hanks' CMFBSS medium with 7.5% inactivated fetal calf serum and 200 units penicillin/200 mg streptomycin. The cell suspensions were adjusted to contain 2 X 10^6 cells/ml and assayed by the lymphocyte transformation technique. The response of lymphocytes to specific antigens or to polyclonal mitogens in vitro is an accepted procedure for assaying immunologic competence of the cell-mediated limb of the immune response. Spleen cells from non-anesthetized normal and tumor-bearing mice were placed in Petri plates and exposed to halothane, oxygen or air for 90 minutes prior to lymphocyte transformation, to determine whether there was a difference between anesthetization in vivo and in vitro.

Results. The stimulation index of lymphocytes from normal C3Hf/He mice exposed to 1.5% halothane anesthesia was significantly less than that of lymphocytes from normal C3Hf/He mice exposed to oxygen (S.I. of 25.3 and 33.6, respectively) ($p<.001$). Lymphocytes from tumor-bearing C3Hf/He mice demonstrated the greatest degree of immunosuppression when compared to those of normal (non-tumor-bearing) mice. That the tumor was the principal immunosuppressive factor was demonstrated by the S.I. of 34.6 for the non-tumor-bearing mouse lymphocytes and 4.1 for those of the mice with fibrosarcomas ($p<.001$). Lymphocytes from tumor-bearing hosts exposed to 1.5% halothane anesthesia demonstrated diminished lymphocyte transformation compared with those from control (tumor-bearing) mice exposed to oxygen (S.I. of 2.6 and 3.9 respectively) ($p<.01$). In both tumor-bearing and normal mice, there was a significant suppression of the cell mediated immune response when the animals were exposed to halothane compared to exposure to oxygen. Results of this investigation demonstrated that halothane anesthesia can potentiate the suppression of cell-mediated immunity observed in tumor-bearing hosts.

Discussion. We have shown that C3H mice bearing fibrosarcomas demonstrate depressed cell-mediated immunity, i.e., depressed transformation of lymphocytes challenged with mitogen, compared with non-tumor-bearing mice of the same strain. Of even greater interest is the observation that these tumor-bearing mice showed significantly greater depression of lymphocyte transformation when they were exposed to halothane anesthesia for 1.5 hours. To determine the potential influence of anesthesia on a patient's neoplasm, one must consider the effects of the tumor cells, as well as the effects on the host immune responsiveness. Experimental studies suggest that anesthetic agents might have antimitotic effects on tumor cells as well as on normal cells, including those that mount an immune response. Antimitotic influence was observed during extended in vitro exposure of cells to anesthetic agents. Animal studies in tumor-bearing hosts have demonstrated effects ranging from inhibition to no effect to enhancement of tumor growth following anesthesia.[3] Both the species and tumor host models may be significant in explaining these differences. Any interference with the immune mechanism by either anesthesia or operation and its stress response may lower the host's resistance or surveillance against neoplasia. Anesthetic agents, both general and local, have been demonstrated to exert an inhibitory effect on the killing of tumor target cells by patient leukocytes in sophisticated in vitro assay techniques. Thus, subjects with severely compromised host resistance and excessive tumor mass could undergo critical depression of host resistance as a consequence of anesthesia.

References.

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