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A997

TITLE: PULMONARY PRODUCTION OF TUMOR NECROSIS FACTOR DURING HALOTHANE ANESTHESIA IN MICE

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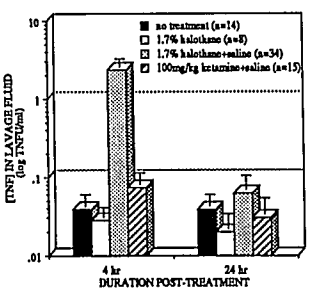
Tumor necrosis factor (TNF), a pleuropotential cytokine released from macrophages and monocytes, is associated with acute phase reactions. TNF's regional effects on combating infectious disease through activation of the regional immune response and on changes in the integrity of the microvasculature are not well understood. This report examines the effect of ketamine and halothane anesthesia on the regional pulmonary production of TNF in mice following buffered saline aspiration into the lungs via the intranasal route.

Mice anesthetized with 100mg/kg ketamine or 1.7% halothane for 2 hours were inoculated intranasally with 50 µl of buffered saline, pH 7.4 (controls included halothane treated and unanesthetized mice not inoculated). Broncho-alveolar lavage (BAL) was performed at 4 and 24 hours post-inoculation. The collected lavage fluid was analyzed for TNF using the WEHI 164 cytotoxicity assay. In a second experiment to verify equal distribution of the inoculum into the lungs of the two anesthetic groups 50 µl of 2% BSA containing 125I labeled albumin was instilled intranasally into 6 ketamine and 6 halothane treated animals. Distribution of the labelled inoculum was assessed by removing the lungs and counting the radioactivity in a gamma counter.

Dissemination of radiolabeled albumin was similar between the two anesthetic groups following intranasal instillation (ketamine: 17.6±4.1%, halothane: 22.2±6.7%). The mice that received halothane and saline demonstrated a large peak of TNF activity (2.3 ± 0.6TNFU/ml) 4 hours after saline instillation (fig.). This peak did not occur in the mice that had received ketamine and saline (0.07 ± 0.03TNFU/ml) or in the mice that received just halothane (0.03 ± 0.01TNFU/ml). At 24 hours, all groups exhibited TNF activity similar to the untreated control animals.

Local pulmonary production of cytokines is important in the regional immune response and in control of the microcirculation. These agents are therefore important in the control of infection and alveolar capillary permeability. The regional response to aspiration of saline, a very mild pulmonary irritant, is different in mice anesthetized with halothane as compared to animals receiving ketamine. The reasons for these differences are not readily apparent although the most likely hypothesis would involve anesthetic induced alteration of activation of lung macrophages to produce the TNF, either directly or indirectly by effects of the anesthetics on other cellular components of the lung. Anesthetic modification of regional production of cytokines, TNF in particular, would be expected to influence the severity of pulmonary complications in the postoperative period. Therefore the choice of the anesthetic agent may be important for the patient at risk of aspiration or other types of intraoperative lung injury.



Regional pulmonary production of TNF following intranasal instillation of buffered saline in ketamine or halothane anesthetized mice, 4 hrs. and 24 hrs. after aspiration.

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TITLE The Effect of Duration of Anesthetic Exposure on Pulmonary Acid Injury

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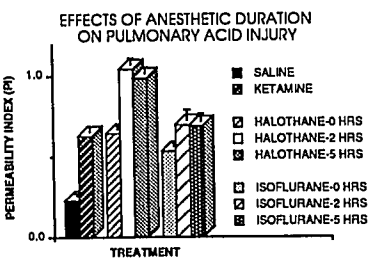
The decision to continue surgery following aspiration of acid into the lung is controversial. In the rat model of pulmonary acid injury there is a progression of the disease from a chemical burn type of injury to an inflammatory response characterized primarily by a neutrophilic infiltrate. The effects of anesthetic agents on this developing inflammatory pulmonary lesion could be expected to play a role in the outcome of the disease.

Long-Evans rats, 300 gm, (n=90 animals) were anesthetized with ketamine, 100 mg/kg IP, 1% halothane or 1.5% isoflurane. Body temperature was controlled at 37°C. Saline/HCL, 1.5 ml/kg; pH=1.25 was instilled through a tracheostomy, control animals received saline alone, pH=5.3. Injury was assessed using a simple ratio of ^{125}I tagged albumin leakage into lung to radiolabeled albumin to the blood (permeability index, PI) five hours after injury. Rats were randomly assigned to one of three groups: 1) animals which were woken up immediately after acid injury, 2) animals that received two hours of anesthesia after acid injury; or 3) animals which received five hours of anesthesia after acid injury. Statistical inference was determined using Students unpaired "t" test corrected for multiple comparisons.



Animals anesthetized with ketamine and allowed to recover immediately had a significantly increased alveolar capillary leak, PI= 0.67±0.04, compared to controls receiving saline, PI=0.23±0.01 ($p<.05$). Animals anesthetized with either halothane or isoflurane and allowed to recover immediately demonstrated similar injuries (PI=0.67 ± 0.03 and 0.73 ±0.08) to the animals that had received ketamine. Animals that received halothane for longer durations of exposure had significant increases in the lung injury at both the two hour anesthesia time and the five hour anesthesia time with PIs>0.90 ($p<.05$) (see table). Rats that received isoflurane for five hours had a less injury than was observed in the group that had received halothane, 0.70 ±0.08 vs 0.99 ±0.07.

These *in vivo* data support the findings from previous experiments in our laboratory which demonstrated that halothane increased oxidant injury in cultured endothelial cells.[1] These results allow us to speculate that volatile anesthetics, halothane in particular, may increase the damage of chemical effectors produced by inflammatory cells both *in vitro* and *in vivo*. These data support the practice of immediately terminating anesthesia, if possible, following aspiration of gastric acid contents into the lung, especially if the complication occurs during halothane anesthesia.

1. *Anesthesiology*, to be published June, 1991.