Title: REGULATION OF DANTROLENE PRETREATMENT IN MALIGNANT HYPERTHERMIA SUSCEPTIBLE PATIENTS USING A PLATELET BIOASSAY

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Introduction. Oral dantrolene sodium has been approved by the FDA as a pre-operative protective agent in malignant hyperthermia susceptible (MHS) individuals. However, recommended dose regimens differ widely (1,2,3,). A diagnostic platelet halothane bioassay (PHB) for MHS has been developed based on the concentration of platelet nucleotides, using the reduction of the ratio between adenosine triphosphate (ATP) plus adenosine diphosphate (ADP) to adenosine monophosphate (AMP) plus hypoxanthine (HYPX) after platelet-rich plasma (PRP) is exposed to halothane. This ratio is reduced three times more in MHS patients than in normals. The assay method will be described briefly in this presentation and in more detail at a later date. This study demonstrates that dantrolene sodium pretreatment normalizes the platelet response of MHS individuals and shows the doses and timing required to achieve this effect in MHS patients.

Methods. We have studied 19 surgical patients, 12 of whom had documented episodes of malignant hyperthermia (MH) and 7 patients with a positive family history of MH, an elevated CPK and a positive PHB. The adult patients received a total of 8 mg/kg orally of dantrolene sodium in two doses of 4 mg/kg each, 9 hours and 2 hours prior to surgery. Three of the 19 patients were children under 10 years of age who received one dose of dantrolene sodium 6 mg/kg orally 9 hours prior to scheduled surgery. Blood samples for PHB were taken prior to the administration of dantrolene sodium and just prior to the induction of anesthesia to determine the platelet reaction to halothane. The PHB was performed on PRP using high performance liquid chromatography to separate and quantitate the purine nucleotides. From one aliquot of PRP, a control ratio R is calculated by the formula:

$$R = \frac{ATP + ADP}{AMP + HYPX}$$

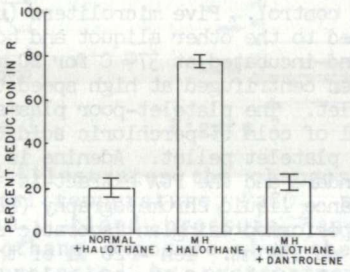
Another aliquot is exposed to halothane to obtain the ratio in the presence of halothane (R_H). The two ratios are compared as follows:

$$\left[1 - \frac{R_H}{R}\right] \times 100 = \% \text{ reduction in R}$$

The anesthesia, preparations of the operating room and anesthesia machine were as recommended by Britt (4).

Results. The mean % reduction of R in the presence of halothane in 23 normal individuals was previously found to be 23.3 + 3 SEM. This value is statistically significant ($p<.0001$) from the mean of 77.95 + 2.52 SEM observed in the MHS group and the MHS related group who were PHB positive. After dantrolene sodium pretreatment, the mean % reduction in R for both MHS groups was 23.25 ± 3.03 SEM which was not statistically different from normals. All 19 patients in this study underwent surgery and anesthesia uneventfully. Muscle weakness was not incapacitating and no pre-operative nausea and vomiting was observed.

Conclusions. We conclude that (1) the platelet halothane bioassay is a reliable index for monitoring safe anesthesia capability in MHS patients and (2) that the dantrolene sodium regimen outlined is safe and satisfactory for proven MHS patients when monitored by the platelet halothane bioassay.



The % reduction in R after the in vitro exposure to halothane observed in normals, MHS patients and MHS patients protected with preoperative oral dantrolene sodium.

References.

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