Anesthesiology
V 75, No 3A, Sep 1991

A302

TITLE: DIAGNOSTIC EVALUATION OF RYANODINE CONTRACTURES IN MHS HUMAN AND PIG SKELETAL MUSCLE

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The use of caffeine and halothane-induced contractures for diagnosis of malignant hyperthermia susceptibility (MHS) may be lacking in sensitivity and specificity. There is evidence for a defect in the single protein molecule referred to as the ryanodine receptor protein, a calcium release channel in MHS human and pig skeletal muscle sarcoplasmic reticulum (SR) (1,2). Ryanodine, an alkaloid that binds avidly to this protein, does so with greater affinity in SR from MHS pig muscle (3) and ryanodine also produces contracture in skeletal muscle. This study tested the hypothesis that ryanodine-induced contracture of MHS muscle may provide a more specific and more sensitive test for MHS. Biopsied muscle from 30 humans and 61 pigs were contracture tested with caffeine, halothane and ryanodine. For pig muscle, concentrations of 0.1, 0.25, 0.5 and 0.75 μM ryanodine were used and for human muscle 0.75, 1.0, 1.5 and 2.5 μM ryanodine were tested. Isometric contracture was measured at 30, 60, and 90 min after addition of ryanodine to the muscle bath. From the halothane and caffeine contracture test results, 3 phenotypes were determined. Phenotypes H and K are MHS and N is not MHS. Ryanodine contractures discriminated best among the pig phenotypes by contracture tensions measured at 60 min. Except for 1 of 30 H-type fascicles tested at 0.1 μM ryanodine, there was no overlap between values for H-type vs N-type pig fascicles. Thus, 1 of a total of 101 H-type fascicles produced a false negative result. Although ryanodine contracture sensitivity of the K-type fascicles is clearly different from the H and N types, there was considerable overlap. This overlap was more toward a positive rather than a negative diagnosis. Only 1 of 55 N-type pig fascicles produced a K-type response and this was from 1 of 10 fascicles tested at 0.75 μM ryanodine. Ryanodine contractures among human muscle were much less specific for MHS discrimination. The overlap between human phenotypes N and H was extensive. For example the number of false MHS results were 4/8, 2/9, 3/9, 4/9 N-type fascicles exposed to 0.75, 1.0, 1.5 and 2.5 μM ryanodine respectively. This lack of specificity for the ryanodine contractures to discriminate N from H-type human muscle may be a consequence of more than one mutation site for MH in humans whereas the ryanodine site may be a single mutation in the pig. Other methods of testing ryanodine contractures are needed before this method is excluded for MHS diagnosis in man.

References
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A303

TITLE: PLASMA LAUDANOSINE LEVELS IN PATIENTS RECEIVING CONTINUOUS ATRACURIUM INFUSIONS DURING ORTHOTOPIC LIVER TRANSPLANTATION

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Atracurium, an intermediate acting non-depolarizing muscle relaxant, would theoretically be an ideal agent in patients with liver disease. It does not depend on the liver for clearance, so its effects should be more predictable in patients with liver dysfunction. However, its principal metabolite, laudanosine, is eliminated primarily through the liver and is a CNS stimulant. Elevated levels of laudanosine have increased anesthetic requirements[1] and caused seizures[2] in animals. This study measured atracurium and laudanosine levels in patients during the 3 major stages of liver transplantation to assess drug and metabolite levels in the presence of major impairment of liver function.

Methods Institutional approval and informed consent were obtained and general anesthesia induced per routine of the attending anesthesiologist. A loading dose of atracurium was followed by continuous infusion to attain steady state. The infusion rate was adjusted to maintain 95-99% muscle relaxation, as judged by peripheral nerve stimulation. Serial blood samples (1.0 ml) were obtained every 15 min during the anhepatic stage and every 30 min during the pre- and postanhepatic stages. Plasma concentrations of atracurium and laudanosine were determined by high performance liquid chromatography. Statistical analysis was done by ANOVA with repeated measures.

Results Atracurium levels did not change significantly over time during the preanhepatic and anhepatic stages (although interpatient variation was considerable); they declined during the postanhepatic stage (see Figure). Laudanosine levels increased significantly during all three stages; mean values did not exceed 0.6 ug/ml.

Discussion Laudanosine levels increased during each of the three stages of liver transplantation, even after the liver had been replaced and atracurium levels were declining. However, the highest laudanosine levels attained in our patients remained considerably below those in ICU patients who showed no evidence of CNS toxicity after 1-4 days' atracurium infusion.[3]

Conclusion Laudanosine is unlikely to accumulate to toxic levels in patients receiving atracurium infusions during liver transplantation.

References 1. Anesthesiology 63:584, 1985. 2. Br J Anaes 59:218, 1987. 3. Br J Anaes 65:829, 1990.

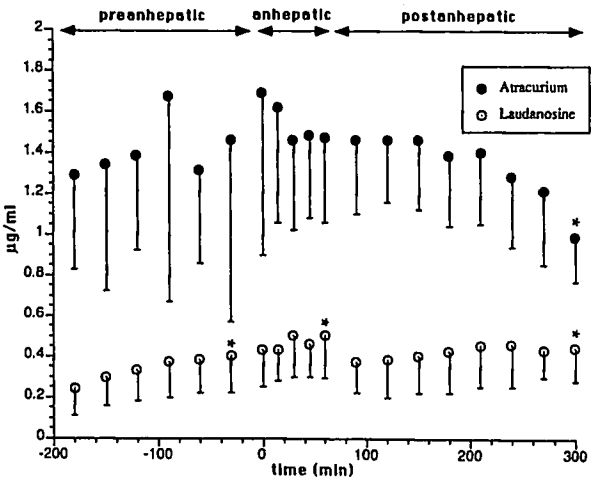

Figure Atracurium and laudanosine levels in plasma of adult patients (N = 15) during liver transplantation. Values shown are means ± s.d.
* = significant (P<.05) change during this stage.