Report of Meeting

VIth international workshop on malignant hyperthermia (MH)

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The VIth International MH Workshop was held in Hershey, PA, on September 16–20, 1992. Over 100 participants from 21 countries met to discuss recent MH research, as well as pertinent clinical issues. This report will summarize important aspects of the meeting.

The keynote address was given by Sidney Fleischer, Ph.D (Vanderbilt), who reviewed the discovery and characterization of the ryanodine receptor, and its function as the calcium release channel in skeletal muscle. The ryanodine receptor is the largest channel structure known, and appears to be the site of the defect in porcine MH and in some cases of human MH. He concluded by listing several other areas where defects in calcium handling may exist in MH, e.g., other receptors (inositol trisphosphate, dihydropyridine), modulators of receptors, or transducer proteins.

Several presentations dealt with the biochemical defect in porcine MH. The ryanodine receptor appears to be "locked" open by halothane, allowing an uncontrolled increase in intramyoplasmic calcium. This sustained calcium elevation leads to muscle hypermetabolism, the hallmark of the acute MH episode. Dantrolene stops the release of calcium by entering the channel and blocking it.

Recently, a single point mutation in the coding for the ryanodine receptor was reported in MH-susceptible (MHS) swine. The so-called "pig mutation," located on chromosome 19q in humans, appears to be present in only 2–7% of MH families in Europe and North America. Dr. Roy Levitt (Johns Hopkins) presented evidence of genetic linkage of human MH to chromosome 17q in five MH families. These important findings confirm that heterogeneity exists in human MH, making it unlikely that a simple genetics test will be available soon. By comparison, the genetic defects that account for 95% of the cases of cystic fibrosis (CF) have been discovered. Only now has a discussion begun on screening the general population for CF.

Under the auspices of the North American MH Registry, an international panel of MH experts has helped develop a clinical MH grading scale. Dr. Marilyn Larach, Registry Director, presented the grading scale for discussion. The scale estimates the likelihood of a suspicious episode under anaesthesia being due to MH, without relying on contracture test results. The scale will enable researchers to use a common clinical definition of MH and to classify patients according to their likelihood of being MHS for comparison with conventional contracture test results, or new tests, e.g., genetics studies.

Dr. Larach also presented Registry data to estimate the sensitivity and specificity of the Caffeine Halothane Contracture Test (CHCT). The sensitivity of the CHCT was calculated to be 100% (95% CI, 88–100%), with a specificity of 78% (95% CI, 71–85%). For clinical diagnostic testing, contracture threshold must be used to maximize sensitivity, to avoid false negative results. However, investigators studying a new MH test, e.g., genetics or magnetic resonance spectroscopy, want high specificity to guarantee that only true positive subjects are present in their "MH(+)" group. Therefore, researchers would use different contracture thresholds, sacrificing sensitivity for a lower false positive rate, to select their subjects.

The controversial issue of masseter muscle rigidity (MMR) was discussed, but no consensus was reached on the acute management of such patients, or on the relationship of MMR and MH. There was some interest in developing practice guidelines for managing MMR.

A panel discussion on MH and neuromuscular disorders was led by Dr. Sheila Muldoon (Bethesda), with the following participants: Drs. Michael Denborough (Canberra), Richard Ellis (Leeds), Gerald Gronert (Davis), Hyam Issacs (Witwatersrand), Renee Krisovic-Horber (Lille), and Frank Lehmann-Horn (Ulm, FRG). The panel concluded that most patients with Central Core Disease are also MH susceptible. However, there is little evidence to support a causal relationship between any other neuromuscular disorder and MH. There was some controversy as to whether acute rhabdomyolysis under anaesthesia in patients with Duchenne dystrophy is a var-

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iant of MH. Although there was consensus that succinylcholine should be avoided in Duchenne patients, there was no agreement whether volatile agents should also be avoided. Dr. Gronert discussed several cases of cardiac arrest and death in children after succinylcholine administration and expressed concern over the continued routine use of succinylcholine in children. Presumably these children had undiagnosed muscular dystrophy, and developed severe hyperkalaemia and rhabdomyolysis.

Finally, Dr. Steven Karan (Bethesda), presented preliminary results on his study of lecithin-coated dantrolene microcrystals. The microcrystals are more soluble than the present commercial preparation, eliminating the need for mannitol and sodium hydroxide. The average initial bolus dose of dantrolene ($2.5 \text{ mg} \cdot \text{kg}^{-1}$) would be contained in a single 5 ml vial, vs 540 ml (nine 60 ml vials) for a 70 kg patient.

The VIIth International MH Workshop will be held on July 16–19, 1994, in Hiroshima, Japan. The Workshop will be held in association with the VIIIth International Congress on Neuromuscular Disease, in Kyoto, Japan, July 10–15, 1994. For more information, contact Dr. Michio Morio, c/o Department of Anesthesiology and Critical Care Medicine, Hiroshima University School of Medicine, Kasumi 1-2-3, Minami-ku, Hiroshima 724, Japan.