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PRELIMINARY OBSERVATIONS ON A NEW SHARK ANESTHETIC, ISOBUTYL m-AMINOBENZOATE

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We have previously shown that MS 222 (ethyl-m-aminobenzoate methane sulfonate) does not produce anesthesia in Squalus acanthias following intravascular injection, although clear-cut surgical anesthesia is elicited when the drug is taken in by respiration. The reason for the difference was that parenteral drug did not reach the brain, whereas drug breathed in rapidly equilibrates among blood, brain, and CSF (Stenger and Maren, Bull. Mount Desert Island Biol. Lab. 7:51, 1967). It was of interest that experiments at the Lerner Laboratory in Bimini gave the same results for the lemon shark; while there was some evidence that the nurse shark was

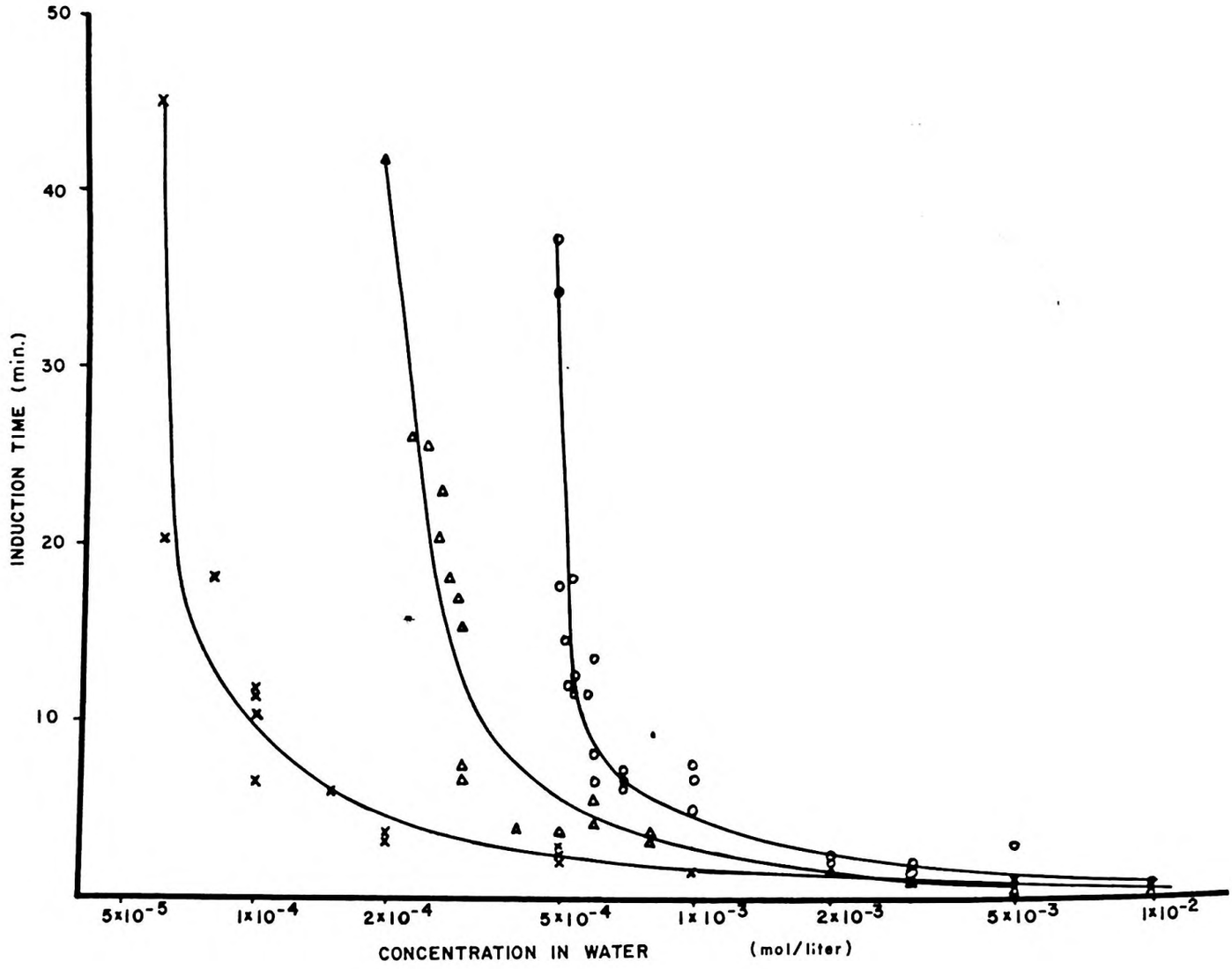

Figure 1. Induction times of goldfish versus molar concentration of MS 222 (0), and the methanesulfonic acid salts of isopropyl m-aminobenzoate (Δ) and isobutyl m-aminobenzoate (x). Each point represents one observation on one goldfish.

susceptible to anesthesia with MS 222 by the intravenous route, and also showed about 20% of plasma concentration in brain and CSF (T. H. Maren and R. H. Maren, unpublished observations).

The isopropyl and isobutyl homologues of MS 222 were synthesized by the method of Adams et al (J. Am. Chem. Soc. 48:1758, 1926) and their anesthetic potency compared with that of MS 222 in goldfish. The fish were placed into beakers containing solutions of the methanesulfonates of the drugs at several different concentrations. The time interval from the first exposure of the fish to the drug solution until the disappearance of its tail reflex was measured. Figure 1 shows these time intervals—"induction times"—plotted versus concentration. The anesthetic threshold concentration is about 60 μM for the isobutyl derivative, 200 μM for the isopropyl derivative and 500 μM for MS 222. Lower concentrations produce only sedation over a 60 min period of observation. With all drugs, increasing the concentration above threshold results in a sharp shortening of induction times until at concentrations of about ten times threshold they become equipotent.

From Figure 1, the isobutyl homologue is about 8 times and the isopropyl homologue about two times more potent than MS 222.

The methane sulfonate salt of the isobutyl homologue was injected over a 10-30 second interval into dogfish via the caudal vein or artery. The fish were in the live-car during the following injection. Nine fish were used. The dosage range was 10-100 mg/kg; at the low side there was no effect, and at the high side fish died. At the 20-50 mg/kg dose range there were profound effects on the central nervous system, none of which were observed in this species following MS 222. Initially, and within 15 seconds of the end of the injection the fish made violent and rapid motions through the water, characterized by rearing and weaving of the head and twisting and plunging of the body. This lasted at most 30 seconds, and was followed by anesthesia, which lasted 1-3 hours. During this time breathing appeared regular, but the fish could not swim, and were flaccid. Most of the fish appeared normal the following day. It appeared that the degree of excitement and of toxicity was in part related to the speed of injection.

It is evident that this drug reached the brain in effective concentrations very rapidly. The difference in parenteral effectiveness between the isobutyl and ethyl esters of meta-aminobenzoic acid may be due to different gill and blood-brain barrier diffusion rates. On the other hand, the isobutyl derivative may have a greater intrinsic anesthetic activity than MS 222. Adams et al (vide supra) have shown in the goldfish that anesthetic potency correlates well with lipid solubility for a series of alkyl para-aminobenzoates. In any event, the isobutyl m-aminobenzoate may prove to be a useful parenteral anesthetic in fish, and the study of its distribution and mechanism of action will be an interesting contribution to comparative pharmacology.

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ATPase ACTIVITY AND SODIUM GRADIENT IN THE RENAL TISSUE OF Psammomys obesus AND Rattus norwegicus

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The role of the inner zone of the renal medulla in the concentrating mechanism of the mammalian kidney is still not well understood. Experimental evidence clearly supports the hypothe-