

Correspondence

Magnesium-ion Physiology

To the Editor:—In the article, "Epsom-salts poisoning and a review of magnesium-ion physiology" (ANESTHESIOLOGY 32: 378, 1970), Dr. Ditzler presents some views about magnesium antagonism which deserve further comment.

First, asystole developing after injection of neostigmine can be better explained by the use of 0.2 mg of atropine only for muscarinic blockade than by an action at the end-plate. Fielder and his colleagues recently demonstrated that neostigmine shifts the dose-response curve of the effects of atropine on heart rate to the right (Fielder, D. L., *et al.*, ANESTHESIOLOGY 30: 637, 1969). Thus, a dose of atropine that would cause acceleration in the absence of neostigmine may now cause slowing in its presence. Second, the proper

dose of calcium needed to antagonize magnesium toxicity usually is judged by the clinical improvement attained. It is possible that not enough calcium ion was given. Magnesium sulfate causes increased urinary excretion of calcium (Nutrition Rev. 26: 12, 1968). Elevated levels of Mg^{++} in blood counteract the increased cardiac automaticity which may result from increased blood levels of calcium (Moore, R. M., and Wingo, W. J.: Amer. J. Physiol. 135: 492, 1942). Both factors permit the clinician to administer more calcium than that amount regarded as "therapeutic."

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Studies of Drug Interaction

To the Editor:—I read with interest the study of the respiratory effects of meperidine and propiomazine in man, by Hoffman and Smith.¹ It is unfortunate that they did not use a factorial design² in their study. This could have been achieved by simply including a placebo as one of the test medications. If this had been done, an analysis of variance, incorporating orthogonal treatment comparisons, would have permitted the authors to test for the significance of the interaction between meperidine and propiomazine without the dubious assumption that placebo would have had no effect. Of course, the additional placebo treatment also would increase the power of the study to detect the main effects of each of the drugs. It would seem that the inclusion of placebo treatment is a *sine qua non* in studies such as this.

A similar criticism applies to the paper by Keats and Telford.³ In the discussion, Hoffman and Smith state that Keats saw no change in the displacement compared with that caused by meperidine alone measured at a ventilation of 8.5 liters. However, if one examines the means as listed in table 2 of the

paper by Keats and Telford, it is clearly evident that the means of the combination of meperidine plus promethazine were higher than for meperidine alone. But, because Keats included neither promethazine alone nor a placebo in a factorial design, he, too, was unable to measure the interaction of these two drugs.

Drug interaction is not a simple field of study. The errors I pointed out in my letter to the editor in 1959⁴ are still made by many clinical investigators.

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