

Physostigmine Reversal of Antihistamine-induced Excitement and Depression

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The antihistamines can stimulate as well as depress the central nervous system.¹ There is no clearcut explanation for these diverse central actions, and no single locus has been agreed upon. Recently we observed a case of excitement and a case of depression following the administration of antihistamines. Both were rapidly reversed by iv administration of physostigmine.

REPORT OF TWO CASES

Patient 1: A 15-year-old white girl who had juvenile diabetes, weighing 120 pounds, was admitted for cystoscopic examination. Diabetes was controlled with 22 units NPH insulin daily. Prior operations included tonsillectomy at 6 and ovarian cystectomy and appendectomy at 13 years of age, both with uneventful halothane anesthesia. Positive laboratory values upon admission were sugar 3+ and acetone + in the urine, and blood glucose 299 mg/100 ml. On the morning of cystoscopy insulin was withheld. Pentobarbital, 50 mg, and diphenhydramine, 50 mg, were given im at 8:00 A.M. At 8:15 A.M. infusion of 5 per cent dextrose in 1/2 physiologic saline solution was started, and thiopental, 150 mg, was given iv for induction of nitrous oxide-oxygen (4:2) anesthesia administered by mask. A single 20-mg dose of succinylcholine was given iv to abolish movement following insertion of the cystoscope. At the end of the 10-minute procedure the patient was responding slightly to verbal commands, but she gradually became unresponsive over the next 5 minutes in the recovery room. The pupils were dilated and fixed, but reacted slightly to light. The face was flushed, and rectal temperature was 101.8 F. Blood glucose was 385 mg/100 ml, but other results of blood studies were within normal limits. During breathing of oxygen by mask, arterial blood-gas values were pH 7.40, P_{O_2} 156 torr, and P_{CO_2} 42 torr. At 9:30 A.M., still unresponsive to verbal commands and painful stimuli, the patient was given physostigmine, 0.3 mg, by slow iv injection. Within 2 minutes she reacted to verbal commands, but remained

sleepy. Three minutes after an additional 0.3 mg physostigmine, iv, she became fully responsive and oriented, and answered questions appropriately. Subsequent neurologic, endocrine and psychological evaluation, including EEG, brain scan, skull x-rays, hormonal assays, EMG, and intravenous amyltal test, disclosed no abnormality.

Patient 2: A 67-year-old white man weighing 160 pounds was scheduled for excision of a cataract in the right eye under local anesthesia. Medical history and physical examination disclosed no abnormality except chronic simple glaucoma, for which the patient was using 1 per cent pilocarpine eye drops. Blood count, urinalysis, electrolyte studies, ECG, and chest x-rays disclosed no abnormality. Meperidine HCl, 75 mg, and promethazine, 25 mg, were given im one hour before operation. In the operating room the patient was quiet and fit-looking; pulse rate was 70/min, blood pressure 150/80 torr. Oxygen, 6 l/min, was given by nasal cannula. Subcutaneous infiltration and retrolubular block, done with 130 mg lidocaine without epinephrine, resulted in satisfactory anesthesia. Three minutes later the operation began. It proceeded uneventfully for about 20 minutes, after which the patient became restless and agitated enough to interrupt the procedure. Diazepam, 5 mg, iv, did not quiet the patient. Arterial blood-gas values were: pH 7.43, P_{CO_2} 35 torr, and P_{O_2} 105 torr. Physostigmine, 1.0 mg, was given by slow iv injection. Within a minute the patient became cooperative, oriented and alert. The cataract operation was continued and concluded without further difficulty.

DISCUSSION

Stimulation of the central nervous system occasionally occurs following administration of conventional antihistamines in sedative or hypnotic doses.¹ Mild central nervous system depression usually occurs after administration of therapeutic doses of antihistamines. Particularly prone to cause CNS depression are the aminoalkyl ethers, such as diphenhydramine.² Many antihistamines possess significant anticholinergic activity. There is no correlation between the CNS effects of antihistamines and their potencies as peripheral histamine antagonists.

Physostigmine, though long well-known as an anticholinesterase inhibitor, has only recently been proposed to reverse anticholinergic delirium resulting from belladonna alkaloid overdose,^{3,4} acute tricyclic antidepressant

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poisoning,⁵ intoxication from asthma powders (stramonium) and sleeping preparations,^{6,7} and phenothiazine- and diazepam-induced coma.⁸ Its use to reverse antihistamine-induced coma or stimulation has not yet been described. Since physostigmine is a tertiary amine, it rapidly crosses the blood-brain barrier. It presumably increases brain acetylcholine activity by inhibiting cholinesterase. Since physostigmine is rapidly hydrolyzed by cholinesterase,⁹ repeated therapeutic doses may be necessary at 30- to 60-minute intervals.

It is unlikely that the severe CNS depression seen in Patient 1 was related to the anesthetic agents used. The time course was compatible with peak effect of diphenhydramine; the depression became progressively worse in the recovery room. The agitation observed in the second case is unlikely to have been a toxic reaction to lidocaine. An intravascular injection would have produced immediate symptoms. Drug absorption from the injection site would produce low blood levels of lidocaine after this relatively small dose, and, any systemic toxicity would have been adequately masked by the diazepam administered. Thus, in both cases physostigmine appears to have counteracted some anticholinergic activity manifested by antihistamines.

In summary, two cases of physostigmine reversal of antihistamine-induced excitement and severe depression are reported. Clinical doses of antihistamines may be relative over-

does for some patients, and may evoke bizarre CNS actions or a clinically significant anticholinergic syndrome. Physostigmine administration is a reasonable addition to the therapy of unexplained agitation or depression occurring after antihistamine administration.

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Erratum

The references for the article "Ketamine and Intraocular Pressure," in the November issue (*ANESTHESIOLOGY* 43:575-578, 1975), are:

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