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Physostigmine Reversal of Benzquinamide-induced Delirium

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There have been numerous reports recently concerning the use of physostigmine in reversal of central anticholinergic syndromes produced by drugs with anticholinergic properties. Benzquinamide, first introduced as a tranquilizer (Quantril®) and now used as an antiemetic agent (Emete-con®), has anticholinergic properties.¹ This is a case report demonstrating the successful reversal of benzquinamide-induced delirium by physostigmine.

REPORT OF A CASE

A healthy, 61-kg, 18-year-old girl was scheduled for diagnostic laparoscopy for evaluation of intermittent abdominal pain. She was taking no medication and had no allergies. Laboratory and x-ray findings were all within normal limits. At 0745 she was premedicated with diazepam, 5 mg, meperidine, 100 mg, and atropine 0.4 mg, iv. At 0800 anesthesia was induced and maintained for one hour with a total of 440 mg thiopental, 15 mg meperidine, and N₂O:O₂, 4:2 l. A 0.2 per cent succinylcholine drip was used for tracheal intubation and muscle relaxation during the procedure. The patient was awake, coherent, and cooperative in the recovery room. At 0915 she complained of nausea without vomiting and received 25 mg benzquinamide as a single dose, iv. Within minutes, the patient complained of "feeling funny," became progressively delirious, and developed involuntary jerking movements of the head and arms. Although the muscular activity appeared similar to an acute dystonic extrapyramidal reaction, the delirium suggested a central anticholinergic syndrome rather than an extrapyramidal reaction. A single dose of physostigmine, 1 mg, was given iv over 1 minute, with clearing of the symptoms in 1-2 minutes. The symptoms did not recur, and the patient had an uneventful recovery.

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DISCUSSION

Benzquinamide is a benzoquinolizine derivative that is chemically unrelated to the phenothiazines or to other antiemetics. It was originally introduced as an anti-anxiety drug in the early 1960's and more recently has been used as an antiemetic agent. Side-effects of the drug include antihistaminic,¹ anticholinergic,¹ bronchodilating,¹ pressor,² respiratory stimulant,³ and extrapyramidal effects.⁵

This case report represents a central nervous system reaction to benzquinamide that was successfully reversed by physostigmine. Since physostigmine is a tertiary amine that readily crosses the blood-brain barrier, it is useful to reverse the central anticholinergic syndrome. It is thought to do this because of its anticholinesterase properties, although it has been suggested that physostigmine reversal of coma and sedation by tranquilizers may be due to a more generalized analeptic phenomenon.⁴ Since benzquinamide has anticholinergic properties and the phenomenon that was seen in this patient was reversed by physostigmine, it is likely that the problem in this patient was the central anticholinergic syndrome.

Benzquinamide has been reported to cause dystonic extrapyramidal reactions reversible by diphenhydramine.⁵ Patients who have this syndrome improve when given anticholinergic drugs and become worse when given an anticholinesterase such as physostigmine.

Thus, benzquinamide, in common with many other tranquilizers, may have two different CNS side-effects upon the patient. The circumstances that cause the central anticholinergic response to a tranquilizer in one patient and the dystonic extrapyramidal reaction in another are not clear. Normal central nervous system control appears to involve a balance between cholinergic and dopaminergic systems. When a drug depresses the dopaminergic

system or enhances the activity of the cholinergic system, there is a dystonic extrapyramidal reaction. When the reverse exists, a depression in the cholinergic system or an augmentation of the dopaminergic system, a central anticholinergic syndrome becomes prominent. Treatment of a patient who has a preponderance of cholinergic activation with a drug such as physostigmine would tend to make the syndrome worse, and is potentially dangerous.⁶ Likewise, treating a patient with a depressed central cholinergic system with anticholinergic drugs such as atropine would make this syndrome worse.

It is important to recognize that tranquilizers such as benzquinamide can produce such a dual response, and that the clinical syndromes may be similar. The central manifestations of the central anticholinergic syndrome are delirium, anxiety, hyperactivity, seizures, hallucinations, illusions, disorientation, and recent-memory impairment.⁷ The extra-pyramidal reaction can consist of akinesia (mask-like facies, rigidity, tremors, lethargy), akathisia (restlessness, inability to sit still), or dyskinesia (dystonia, hypertonicity of muscle groups).⁸ With the extrapyramidal reaction, consciousness is not impaired, an important difference between the two CNS reactions. In our case the diagnosis of central anticholinergic syndrome was made because of impairment of consciousness. Therefore, physostigmine was used to reverse the reaction successfully. The picture could have been clouded by the other drugs the patient received prior to the benzquinamide, especially diazepam and atropine, which have similar CNS effects and can be reversed by physostigmine.^{9,10} However, the temporal relation between injection of benzquinamide and the onset of symptoms implicates benzquinamide as a major contributor to the reaction.

Physostigmine is a useful anticholinesterase in a situation such as this: it is a tertiary amine that easily crosses the blood-brain barrier because of low ionization, whereas most other anticholinesterases are highly ionized quaternary amines that do not readily cross the blood-brain barrier.

Physostigmine has been reported to reverse the central anticholinergic syndromes caused by belladonna drugs,^{10,11} the tricyclic antidepressants,¹² phenothiazines,⁴ and antihistamines,¹³ and the coma and delirium that can result from benzodiazepines.^{9,14} Benzquinamide can be added to the list of drugs whose actions can be reversed by physostigmine.

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