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SEIZURE DUE TO DIPHENYLHYDANTOIN-METHYLPHENIDATE INTERACTION

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ABSTRACT

Signs and symptoms of DPH toxicity were seen in an epileptic child who had received DPH and MP concurrently. In the absence of liver and kidney disease and any intercurrent infection, and with the patient's recovery following the withdrawal of DPH, it appears that drug-drug interaction is the most logical explanation for DPH intoxication.

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INTRODUCTION

Since its introduction for management of seizure disorders in 1938, diphenylhydantoin (Dilantin, DPH) has been found very effective for the treatment of grand mal and autonomic epilepsy.

On the other hand, DPH treatment is associated with a large number of side effects, some of which may be a threat to the patient's life and occasionally have been fatal.[2]

We report a patient who developed DPH toxicity while receiving combined DPH and methylphenidate (MP) treatment.

CASE REPORT

A 10 year old boy was brought to the emergency room of Mofid Children's Hospital, Tehran, and was subsequently admitted following a generalized convulsion.

He was a known case of seizure disorder, who during the preceding one and a half years, had several episodes of grand mal seizure. No aura or localizing features had ever been present. After suffering repeated episodes of generalized tonic-clonic convulsion, his seizure came under excellent control with phenobarbital. A few months later, the child was dismissed from school because of extreme hyperactivity.

To eliminate this new problem, the patient's medication was changed to DPH and phenobarbital was gradually discontinued. After being well behaved for a period of time, overactivity once again became a matter of concern for both teacher and parents. He was given methylphenidate (Ritalin) 10 mg twice daily for the hyperkinetic reaction. At that time, he was on DPH 8mg/kg/24 hours (200mg DPH) and the blood Dilantin level, immediately before initiation of Ritalin treatment (estimated by gas chromatography), was 11.9 mcg/ml. About a month later, on the day of admission, the child returned from school complaining of dizziness, headache and nausea. Within a couple of hours, he went into a tonic-clonic seizure and was subsequently rushed to the emergency room. Upon admission, his vital signs were stable but his speech was slurred and he had great difficulty in comprehending and answering questions. Intermittent purposeless movements of the limbs, horizontal nystagmus, frequent lip smacking and a tendency to fall asleep were noted. The patient experienced many brief generalized seizures during the twenty four hours following admission.

The results of CBC, urinalysis, routine chemistry, chest and skull X-ray, ECG and cerebrospinal fluid examination were all within normal limits. Immediately after admission, blood was sent for a DPH level. Viral studies for herpes, mumps, CMV, echo, coxsackie, and measles were undertaken and subsequently all returned negative. Electroencephalogram revealed diffuse slowing and a mixture of 2-5 CPS high voltage delta and theta waves. In view of increasing seizure activity, the patient's Dilantin was increased to 12 mg/kg/day and because of his unresponsiveness which developed the day after admission, it was given intravenously. Thirty hours after admission, the result of

DPH level (taken on admission) was reported as 56 mcg/ml. Dilantin was completely discontinued and he was maintained on intravenous fluid therapy.

The course of recovery was gradual and two days after discontinuation of Dilantin, the patient was well and ambulatory. DPH level 48 hours following its termination was reported as 20 mcg/ml. Five days later, the boy was discharged and his mother was instructed to reinstate DPH as before. To counteract the patient's hyperactivity problem, diphenhydramine was prescribed. During the past several months, up to the writing of this article, the child has been on combined DPH and diphenhydramine (Benadryl) and has continued to be seizure free with no problem of hyperkinesis.

DISCUSSION

Studies by several investigators revealed that DPH is parahydroxylated in the liver and a large proportion of it is excreted in the urine as 5-hydroxyphenyl-5-phenylhydantoin (HPPH).[3,4]

Both genetic and environmental factors can effect the final fate of DPH and its half life and blood level. Among intrinsic factors, deficiency of hydroxylating enzymes and among extrinsic or evironmental factors, intercurrent infections should be mentioned.[5-7]

Sevensmark and Buchthal[8] reported three children who developed high serum levels of DPH without change of treatment during intercurrent infections.

In our case, because of sudden alteration of state of consciousness, behavior change and seizure, the possibility of encephalitis was strongly considered.

Electroencephalographic findings in this case could be compatible with encephalitis. Gibbs and Gibbs[9] found high voltage slow activity as a usual EEG pattern of acute encephalitis. However, lack of fever during the entire illness, normal cellular and chemical characteristics of C.S.F., negative viral studies and course of the illness were all against that diagnosis. High DPH levels in the patient's serum at the time of seizure and the patient's recovery following the discontinuance of DPH, proved that the child's presenting symptoms were manifestations of DPH intoxication.

As DPH toxicity had occurred when the patient had received combined Dilantin and Ritalin, in the absence of any intercurrent infection and without any change in DPH dosage, there can be very little doubt that DPH-methylphenidate interaction produced such toxicity.

We have been able to find only one previously reported case of DPH-MP interaction: Garretson, et al.,[10] described a five year old Negro boy who received DPH and Primidone for grand mal epilepsy and who developed ataxia following administration of methylphenidate. The patient's DPH level rose from 8.6 mcg/ml to 35 mcg/ml. Mirkin and Wright[11] studied interaction of DPH and MP in normal subjects and found that oral administration did not elevate the plasma level or prolong the plasma half life of DPH beyond the value obtained when DPH alone was administered. But in a patient with seizure disorder who was on Dilantin and other anticonvulsants, symptoms of DPH toxicity were observed when the patient was treated with MP, and plasma DPH levels increased from 14 mcg/ml to 29 mcg/ml.

Kupferberg et al.,[12] did not detect MP-induced alteration of the plasma anticonvulsant level, but they concluded that because of the limited number of studied patients, the possibility of interaction of MP with anticonvulsants could not be ruled out.

Review of this data suggests that inhibition of DPH metabolism by MP is not a generalized phenomenon. In view of the increasing popularity of psychostimulant drugs in the management of hyperkinetic children, the possibility of such interaction should be borne in mind.

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