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OPTALIDON POISONING IN CHILDREN: A STUDY OF TWENTY CASES

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Optalidon[R] is a mixed sedative-analgesic-antipyretic drug which enjoys great popularity at the present time in Turkey as well as in many parts of Europe. It contains isobutylallyl-barbituric acid (Sandoptal [R]), 50 mg; trimethyl-xanthine (caffeine), 25 mg; and phenyl-dimethyl-aminophenazone (aminopyrine, Pyramidon [R]), 125 mg. In spite of apparently extensive use of the drug for many years, there is little to be found in the medical literature dealing with the nature of accidental overdosage in children. Romagny et al.[1] reports five cases seen in a pediatric service over a period of two years. These authors noted the lack of medical literature in cases of poisoning by this compound, and they discuss the variable nature of the symptoms resulting from the combination of the three component drugs in Optalidon. We know of no other reports of accidental poisoning in children by this medication. The present report describes the clinical features of 20 such cases seen over a period of the last four years in this hospital.

Description of Cases

The children in this group ranged from one year to ten years of age. Twelve of them were male, eight were female. More than half

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Optalidon is made by Sandoz Pharmaceutical Company, Limited Basle, Switzerland.

the group (eleven) were observed in the seven-month period from October 1963 to the time of writing. We attribute this to the careful notations made in cases of poisoning during this time in the hospital out-patient department, rather than to increased use of the drug. The other cases were scattered over the years from 1960 to October 1963 and were found in the hospital archives.

The number of tablets thought to have been ingested is shown in Table 1, and a rough estimate of the dosage of the barbiturate component per kilogram is given. This is admittedly open to considerable doubt, particularly as vomiting occurred spontaneously in some cases, thus reducing the actual amount absorbed.

The time elapsed from ingestion to attendance at the hospital ranged from one-half hour to 24 hours. It is notable that eleven patients were seen more than three hours after ingestion, a time lapse sufficient to allow for the complete absorption of the drug from the alimentary tract.

Symptoms

Three symptoms predominated: 1. *Drowsiness* was noted in 15 cases. The five cases in which it was not recorded are, with one exception (case 9), those patients who were brought to the hospital for attention within one hour after ingestion. 2. *Ataxia*, symptoms of incoordination of movements of the extremities, and difficulty or inability in walking unassisted, were noted in 14 of the 20 patients. These symptoms varied in intensity. 3. *Excitement*, agitated behavior, restlessness and irritability, in several cases intense enough to be called delirium, were observed in nine of these children. Vomiting occurred in three cases prior to admission and in one following admission. There were no other pertinent symptoms recorded in any of the hospital notes.

Physical Observations

In addition to the notations regarding the state of consciousness the agitated behavior and ataxia, the following physical observations are worthy of mention: 1. *Deep tendon reflexes* were noted to be absent in five cases, and depressed in an additional four cases. Two patients had a positive Babinski response. 2. *Pain response* was absent in only four patients, with a diminished response in one other. Corneal response to touch was absent in four patients. 3. *Vital signs* were checked and shock and hypotension were not observed. In three cases there was tachycardia.

TABLE I

SALIENT FEATURES OF 20 CASES OF OPTALIDON POISONING

Case number	Initials	Age	Sex	Date	No. of pills	Weight in Kg.	Dose mg/kg barbiturate	Interval to admission hrs.	Symptoms				Findings		Treatment				Remarks
									Drowsiness	Ataxia	Excite-ment	Vomiting	Reflexes	Pain Response	Lavage	Caffein	I. V. Fluids	Hrs. to Improve-ment	
1	G.E.	10/12	M	1962	11	7.8	70	7.5	+	0	0	+	0	0	0	+	+	12	
2	B.E.	1.5	M	1962	3	13	11	.5	+	+	+	0	↓	+	+	—	+	12+	Babinski response noted on admission
3	G.M.	4	F	1961	22	12.8	91	8–10	+	0	+	—	0	0	0	+	+	48	Diagnosis of "Status epilepticus" made on admission. Corneal response absent
4	K.C.	10	M	1964	6–10	27	15	15±	+	+	0	—	+	+	0	0	+	24	
5	P.T.	4	F	1962	?	15.4	?	2	+	+	+	—	+	+	0	0	+	12+	Brain trauma suspected Babinski response noted
6	B.S.	3	F	1961	8	12.5	32	.5	0	+	+	+	+	+	+	+	+	24	
7	Y.M.	3	M	1961	8–10	12.9	34	8.5	+	0	+	0	0	+	0	+	+	48	
8	H.N.	2.5	F	1960	4	12	16	4.5	+	+	0	0	↓	↓	0	0	+	4–6	
9	E.S.	1.25	F	1964	3–4	11.9	15	5–6	0	+	++	0	+	+	0	0	0	—	Not admitted
10	Y.S.	1	M	1963	3–4	9.6	18	.5	0	+	+	0	+	+	+	0	0	10+	Not admitted
11	K.N.	1.5	F	1963	2–3	10	12	1.5	0	+	+	0	+	+	+	0	0	—	Not admitted
12	A.A.	6	M	1963	5	16	14	.5	+	0	0	0	+	+	+	0	0	—	Not admitted
13	E.S.	3	M	1963	4	14	15	1	0	+	0	0	+	+	+	0	0	—	Not admitted
14	M.K.	6	M	1964	10	20	25	24	+	+	0	+	+	+	0	0	0	48+	Not admitted
15	M.Y.	3.5	M	1964	9	15	30	.75	+	+	0	0	↓	+	+	0	+	36	
16	B.Y.	5+	M	1963	?	15	?	2.5	+	+	0	0	↓	+	+	0	0	—	Not admitted
17	O.A.	5	F	1963	?	16	?	5.5	+	+	+	0	+	+	0	0	+	24	
18	M.Y.	2	M	1963	10+	10.8	50+	7	+	0	0	0	0	0	0	0	+	48+	Comatose, no pupillary reflexes
19	T.Z.	5.5	F	1964	7–8	15	27	3–4	+	+	0	0	+	+	0	0	0	24	Ataxia evident 40 hrs. after ingestion
20	O.K.	4.5	M	1964	?	18	?	6	++	0	0	0	0	0	0	0	+	24	Head injury suspected, comatose, no corneal or pupillary response

Laboratory Observations

Determination of barbiturates or other components of the compound in the urine were not performed. There were no remarkable changes in the hemoglobin or white blood cell counts, nor was eosinophilia observed.

Management

Thirteen of the 20 cases were admitted to the hospital. Six were deemed not critical enough to be admitted and were sent home. Most of these did not return for follow-up. One case (number 9) was refused admission by the parents and was taken home. There was no follow-up. Intravenous fluids were given to 12 of the patients admitted, usually for six to 12 hours. Four patients received stimulant doses of caffeine. One patient (number 6), who became drowsy sometime after admission, was also given caffeine. This stimulant was given more than once to only two patients, (numbers 3 and 7), who received 3 and 4 doses, respectively. Strychnine, picrotoxin and other analeptics were not used at all. Gastric lavage was carried out in only eight patients who were seen within several hours of ingestion. Patients who had ingested the poison three or more hours prior to hospitalization were not lavaged.

Duration of Symptoms

Where the information is available and reasonably accurate, it is apparent that the state of drowsiness lasted at least three hours and as long as 11 to 24 hours in some cases. Ataxia and unsteadiness persisted longer, generally up to 48 hours, and in many cases was still quite obvious at discharge several days following admission. To our knowledge none of the patients have had any persistent symptoms or sequelae.

Discussion

The common use of this medication in Turkey unquestionably plays a role in the frequent occurrence of accidental ingestion and subsequent poisoning. The attractive, pink, sugar-coated tablets are tempting to most children. It is interesting to note in this connection a study by Jolly and Forrest,[2] in which pink was found to be the second most popular pill color among children, out of a selection of ten different colors. Furthermore, the prospectus inclosed with the medication

gives no warning of any potential hazard to children. The dosage for children is given as "1-3 tablets daily according to age."

In two of the cases in our group (numbers four and fourteen) medication had been given by the parents for headache and toothache, respectively. These children continued to ingest the drug of their own volition. The latter case is worthy of some description.

This six year old boy developed a toothache two days prior to observation. For this he was given one Optalidon tablet. The next day, because the toothache continued, he took ten more tablets unbeknownst to his parents. One and a half hours later, at suppertime, he became drowsy and somewhat disoriented. He took only a glass of milk and promptly went to sleep. The next morning at six o'clock he awakened, was very irritable, and began to thrash about in his bed. He vomited several times. He was very unsteady and ataxic, and experienced difficulty in holding his head up throughout the day. Because of severe involuntary movements of all his extremities, he was seen by three different physicians, one of them a neurologist who suggested a diagnosis of chorea. A fourth physician, who had previously seen cases of Optalidon poisoning, suggested this possibility to the parents who then found the open vial of tablets and obtained a clear picture of what had occurred from the child himself. The patient was managed conservatively at home, with no further drugs given, and the symptoms subsided gradually over the next 48 hours. However, he was still slightly ataxic when one of us (I.B.) examined him three days after the ingestion.

Other neurological conditions were suspected among cases in this group. In two (numbers 5 and 20) the possibility of a head injury was entertained. Skull films and lumbar punctures were made with negative results, and in both cases the true nature of the incident was clarified only by careful and persistent questioning of the family. Another child (case number 3) was unconscious on admission, was extremely agitated and appeared to have "cramps". She had fallen a few hours before and "status epilepticus" was suspected. She was given a dose of diphenylhydantoin sodium, but it was only by further questioning and search for the open vial at home that the situation was finally clarified. Accurate diagnosis is often delayed, as others have previously noted, because parents are sometimes reluctant to admit to such accidents having occurred.

Pharmacologic Considerations

The barbiturate component of Optalidon, isobutyl-allyl-barbituric acid (Sandoptal [R]) is classed by Goodman and Gilman [3] as one of

the intermediately rapid-acting barbiturates along with amobarbital sodium (Amytal ® sodium), becoming effective three to six hours after ingestion. Pentobarbital Sodium (Nembutal ® Sodium) and secobarbital (Seconal ®) are considered short-acting members (less than three hours), and phenobarbital (Luminal ®) long-acting. The hypnotic dose of isobutyl-allyl-barbituric acid is about twice that of phenobarbital, secobarbital and amobarbital.[3] A safe daily dosage for children would therefore be about 12 mg per Kg.

Among children, sensitive adults, and some patients suffering from pain it is not unusual to encounter paradoxical side effects (excitement, restlessness and occasionally delirium) in using barbiturates. However, toxic doses more often produce central nervous system depression, a reduction in respiratory minute volume, and occasionally shock with capillary dilatation. Pupils may be constricted or dilated, deep tendon reflexes may be lost or remain intact in spite of coma and a Babinski response may be elicited.

The absorption and action of caffeine (trimethyl-xanthine) is considerably more prompt than the barbiturate component. Studies show that after oral ingestion maximal plasma levels are reached in one hour.[4] Its general stimulant action on the central nervous system is well known. The recommended therapeutic stimulant dose of 8 mg per Kg[5] was reached or exceeded in the majority of these cases. The symptoms of overdosage and side effects, including palpitation, insomnia, nausea, vomiting, headache, vertigo, restlessness, anxiety, and at times delirium, are not unlike those reported in some of these patients.[6] Further toxic affects are tremors of the jaw and extremities which may occur and were observed in one case (number 3), whose reported ingested dose was the highest in the group. It is perhaps significant of the differential absorption rates of caffeine and barbiturate that, the four patients who came to the hospital soon after ingestion of the tablets (numbers 6, 10, 11 and 13) did not exhibit any sedation at the time of arrival, although they were unsteady, irritable and excited. Some degree of sedation occurred in these patients later and one (number 6) was even given caffeine intramuscularly a few hours after admission.

The third component of this medication, aminopyrine (Pyramidon ®, aminophenazone), is an analgesic and, to a lesser extent, an antipyretic. It is completely absorbed from the gastrointestinal tract and peak plasma levels are reached two hours after ingestion.[3] The action of the drug is produced, it is thought, by vasodilation.[4] Large doses can cause cerebral stimulation, convulsions, disturbances in

reflex excitability, and collapse.[7] Beckman[8] recommended a daily dosage of 1.5 to 2.0 Gm for children, or approximately 100 mg per Kg per day. Romangny[1] states that 50 to 100 mg per dose per year of age should not be exceeded. It is possible that with the dosages involved in the cases reported here some of the excitation may be attributable to this drug.

Perhaps a more disturbing feature of aminopyrine is its tendency to produce an isolated agranulocytosis in certain sensitive individuals.[9,3,6] In one group of 960 patients receiving this drug for rheumatic fever, eleven (1.1. %), developed granulocytopenia. In the same report it was estimated that in England in 1951 there were 50 deaths attributable to this drug. The condition has been well studied and appears to occur quite independently of any depressive effect on the other red or white cell elements.[3] Furthermore, those individuals who are sensitive to the drug may develop agranulocytosis after ingesting minute amounts.[3] It is perhaps noteworthy that the sale of aminopyrine is prohibited in England, Denmark, the United States, and perhaps other countries.

Regarding the treatment of the cases reported here, none received any more specific therapy than stimulant doses of caffeine. In spite of some large dosages ingested it is of interest to observe that in only five cases did the deep tendon reflexes disappear completely, a fact which may be attributed in part to the composition of the medication, containing, as it were, its own antidote: a stimulant-sedative mixture. In respect to the management of barbiturate intoxication, much has been written regarding the use of analeptic agents such as picrotoxin, megimide (beta-ethyl-beta-methyl-glutanimide), strychnine, and caffeine. Interesting in this regard, however, is a report of a series of 95 patients who became unconscious after barbiturate ingestion, and were all managed conservatively without the use of any analeptics whatever.[10] In this group, primary attention was directed to a clear airway and maintenance of adequate respiration and there was only one death. The investigators further demonstrated that cardiovascular collapse, when it occurs, can be adequately managed by the use of intravenous neosynephrine or norepinephrine.

Conclusions

Accidental ingestion of Optalidon among children in Turkey is not at all uncommon. An overdose of this drug is capable of producing a clinical picture of excitement, ataxia and somnolence, which in some

of the cases here reported was confused with epilepsy, head trauma and chorea. Although this group of patients suffered no permanent damage or death, it is possible that more grave consequences might occur. It is felt that more cautious labelling and a less attractive tablet might lessen the danger.

Summary

The present report deals with the clinical findings, course of illness and management of 20 cases of acute accidental ingestion of a proprietary preparation, Optalidon [R], containing isobutylallyl barbituric acid, aminopyrine, and caffeine. All of the patients survived. The side affects and hazards of the constituent drugs are discussed.

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