Salicylates and Hypoglycemia

DURING the past 18 months we have seen three patients who developed hypoglycemia in association with salicylate ingestion. The purpose of this paper is to emphasize the importance of considering and recognizing this association. It was possible to perform extensive studies on only one of these patients (case 1); this case will be presented in some detail and the other two only briefly.

Report of Cases

Case 1.—This 22-month-old white male was the product of a normal pregnancy which was complicated by toxemia and abruptio placenta. His birth weight and length were 1.5 kg (3lb 13oz) and 41 cm (16 inches), respectively. The first 48 hours of life were complicated by respiratory distress, recurrent apnic spells, and generalized seizures. A blood sugar value at this time was 4 mg%. The hypoglycemia was adequately controlled with hydrocortisone therapy. At 2 weeks of age, the patient developed unexplained jaundice, associated with hepatitis-like symptoms, which cleared spontaneously. Phenobarbital therapy, instituted at 48 hours of age, was discontinued at 1 month of age; at 13 months of age, tapering of the dose of hydrocortisone was begun because of the initial appearance of cushingoid features. On three occasions, at 16, 18, and 20 months of age, respectively, a single generalized seizure occurred. Each of these seizures was associated with an upper respiratory infection; blood and spinal fluid glucose levels were normal at these times. The patient’s mental and motor development have been normal, with the exception of delayed walking without support because of residual spasticity in the right lower extremity. The physical examination at 21 months of age was normal with the exception of a first degree hypospadias and the spasticity of the leg. His linear growth from birth has been at a constant rate below the third percentile. The laboratory studies performed through 21 months of age had not yielded a specific cause for his hypoglycemia. When the patient was 21 months of age, the history was obtained that the mother had been administering to the patient 60 to 130 mg of aspirin daily since the age of 5 months for “irritability, teething, sleeplessness, etc.” The question then arose whether this patient’s hypoglycemia might be related to salicylate ingestion, and he was admitted to the Clinical Research Center to investigate the possibility.

The data presented in Fig 1 and 2 were obtained during two aspirin-response tests performed during this hospitalization and another one three weeks later. The patient’s nutritional status was normal for the two control and test periods, and ketonemia was absent. The aspirin was administered after an eight-hour fast, and the fast was continued until the end of the control and test periods. At the times of these tests, the patient was receiving 4 mg of hydrocortisone daily, administered orally in four equal fractions; the identical dose and dosage schedule were maintained during the control and test periods. Aspirin, 300 mg in 250 ml of water, and 250 ml of water were given by gavage on each of the two test and control days, respectively. As shown in Fig 1, the blood glucose values during the two control periods varied little from the respective normal fasting blood glucose values; in addition, no symptomatology occurred during the two control periods. In contrast, the blood glucose values fell to hypoglycemic levels during both of the aspirin-response tests. As a fact, both of these tests had to be terminated because of hypoglycemic symptomatology at three and five hours, respectively, after the gavage. During one response test, the blood glucose fell to 17 mg%, severe lethargy and irritability occurred; these same symptoms and a generalized seizure occurred during the second response test as the blood glucose fell to 5 mg%. On each occasion, the symptoms cleared immediately following the intravenous administration of 20% glucose. As shown in Fig 1, the blood salicylate levels during the two response tests did not reach toxic or even high therapeutic levels.

The data in Fig 2 depict the blood insulin levels as determined during one of these response tests; no significant change in these levels was noted either before or during the period of hypoglycemia induced by salicylate administration.
Summary

Case reports are presented of three children who developed hypoglycemia in association with salicylate ingestion. In one patient, it was demonstrated that hypoglycemia could be induced by a small dose of aspirin and that the mechanism of the hypoglycemia did not involve increased blood insulin concentration.

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Generic and Trade Names of Drugs

Hydrocortisone—Cortef, Corteo, Contri, Hydrocortone, Hydrocortone

REFERENCES


Comment

Hypoglycemic symptoms in children receiving salicylates have not been reported frequently in the English literature. In 1960, Mortimer and Lepow described four cases of fatal hypoglycemia associated with varicella and salicylate administration; blood salicylate levels were not measured in these patients. They also presented preliminary laboratory investigations which associated the administration of salicylates in experimental animals with hypoglycemia and a diminished hyperglycemic response to epinephrine. Barnett et al demonstrated hypoglycemia during the course of therapy for acute salicylate intoxication in one patient, although the peritreatment blood sugar value was normal.

Although, in case 1, hypoglycemia had been documented during early infancy, this had been controlled clinically and by laboratory tests for many months prior to the aspirin response tests. The data presented concerning case 1 do not constitute proof that the hyperinsulinemic blood levels and symptoms during these tests were caused by the administration of a subdose of aspirin, but it seems highly probable that such is the case. In contrast to case 1, the other two patients did not have a history suggesting a hyperinsulinic state prior to their salicylate intoxication; it seems reasonable, therefore, to relate their hypoglycemia to the ingestion of aspirin.

That salicylates profoundly affect carbohydrate metabolism has been known for many years. The metabolic derangements associated with salicylate intoxication in human subjects and/or experimental animals which have been postulated as contributing to the associated hypoglycemia include starvation, acidosis, ketosis, depletion of liver glycogen, increased oxygen uptake and glucose utilization, and interference by salicylate with the enzyme systems which produce high energy phosphate bonds. This latter mechanism could increase the utilization of glucose via the tricarboxylic acid cycle, resulting in glycogen deposition and hypoglycemia. The conditions and results of the two aspirin response tests in case 1 demonstrate that hypoglycemic symptoms and blood levels can be associated with ingestion of salicylates in amounts giving salicylate blood levels below the toxic range, and in the absence of an abnormal nutritional, fluid and electrolyte, or acid-base state. The blood levels of insulin did not increase during the one aspirin response test in which they were measured, indicating that elevated blood insulin levels are not the mechanism of salicylate-induced hypoglycemia in this patient. Indirectly, therefore, the data support the hypothesis advanced by others that the hypoglycemia associated with salicylate ingestion results from interference with key enzyme systems.

On the basis of the experience with these three patients in a relatively brief period of time, it would seem that perhaps the occurrence of hypoglycemia following salicylate ingestion is more common than the paucity of reports in the literature would indicate. Awareness of this association will aid in the recognition of hypoglycemia in those patients in whom it does occur. Since the symptomatology of salicyltism and hypoglycemia may be so similar, both conditions should be considered in the evaluation of any appropriately symptomatic child who has received toxic or subtoxic doses of salicylates, irrespective of the child's age or nutritional status.