relied on to establish definitively the diagnosis of debrancher enzyme deficiency.

Summary

A patient with type 3 glycogen storage disease, confirmed by hepatic enzyme assay, is presented. In this patient, the results of the "double barrel" glucagon test were not consistent with those previously reported in this condition and failed to establish the correct diagnosis. Therefore, this test alone should not be relied on to differentiate the various types of this disease.

This work was done during the tenure of a traineeship in Pediatric Endocrinology and Metabolic Diseases, NIAMD training grant No. 2T1-AM-5190 (Dr. Limbeck). A portion of this work was conducted through the Clinical Research Center Facility of the University of Washington supported by the National Institutes of Health (grant FR-37). It was supported in part by a training grant in Pediatric Endocrinology and Metabolic Diseases (National Institute of Arthritis and Metabolic Diseases training grant No. 2T1-AM-5190).

REFERENCES

1. Cori, G. T.: Glycogen Structure and Enzyme Deficiencies in Glycogen Storage Disease, Harvey Lect 48:145-171, 1954.
2. Hug, G.: Glucagon Tolerance in Glycogen Storage Disease, J Pediat 60:545, 1962.
3. Hug, G., et al: Cori's Disease (Amylo-1,6-Glucosidase Deficiency): Report of Case in Negro Child, New Eng J Med 268:113, 1963.
4. Kaye, R., et al: Response of Blood Glucose, Ketones, and Plasma Nonesterified Fatty Acids to Fasting and Epinephrine Injection in Infants and Children, J Pediat 59:836, 1961.
5. Vassella, F.: Die Glucagonbelastungsprobe beim gesunden Kind, Helv Paediat Acta 12:331, 1957.
6. Illingworth, B., and Brown, D. H.: Action of Amylo-1, 6-Glucosidase on Low Molecular Weight Substrates and Assay of This Enzyme in Glycogen Storage Disease, Proc Nat Acad Sci USA 48:1619, 1962.
7. Hers, H. G.: Advances in Metabolic Disorders, New York: Academic Press, Inc., 1964, vol 1, pp 1-44.
8. O'Brien, D., and Ibbott, F. A., ed.: Laboratory Manual of Pediatric Micro- and Ultramicro-Biochemical Techniques, New York: Paul E. Hoeber, Inc., Medical Book Dept. of Harper & Row, Publishers, Inc., 1962, p 134.

Salicylates and Hypoglycemia

GEORGE A. LIMBECK, MD; ROGELIO H. A. RUVALCABA, MD; ELLIS SAMOLS, MD; AND VINCENT C. KELLEY, MD, SEATTLE

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 term pregnancy which was complicated by toxemia and abruptio placenta. His birth weight and length were 1.5 kg (3½ lb) and 41 cm (16 inches), respectively. The first 48 hours of life were complicated by respiratory distress, recurrent apneic 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 hepatosplenomegaly, which cleared spontaneously. Phenobarbital therapy, instituted at 48 hours of age, was discontinued at 5 months 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 150 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 ketonuria 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. In 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, as 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 50% 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[1]; no significant change in these levels was noted either before or during the period of hypoglycemia induced by salicylate administration.

After these studies were completed, all necessary precautions were taken to insure that the patient would not receive any additional salicylate, and his hydrocortisone therapy was tapered and discontinued. During the subsequent three months, the patient has experienced neither hypoglycemic symptomatology nor seizure activity.

Received for publication Aug 10, 1964.

From the Division of Endocrinology and Metabolism, Department of Pediatrics, University of Washington.

Reprint requests to Seattle, Wash 98105 (Dr. Kelley).

Case 2.—This 12-month-old white male was admitted to the Children's Orthopedic Hospital and Medical Center after a six-day illness characterized by fever, increasing irritability and lethargy, and hematemesis. The history and physical examination did not suggest post or present liver or kidney disease. On admission, he was afebrile, tachypneic, and semicomatose. A lumbar puncture revealed clear fluid with ten mononuclear cells, a protein of 20 mg%, and a glucose value of 10 mg%. A simultaneous blood glucose value was zero. The spinal fluid and blood cultures were sterile. In spite of intensive therapeutic measures, his condition progressively worsened and he died 31 hours after admission. The autopsy examination demonstrated cerebral edema as the only abnormality. Cardiac blood obtained immediately after death contained salicylate in the concentration of 6 mg% although the patient did not receive salicylate during his hospitalization. If the formula of Done[2] were applied to this postmortem salicylate value, the estimated serum salicylate concentration on admission would be approximately 18 mg%. Retrospectively, a history was obtained of the administration of 400 to 750 mg of aspirin per day for five days prior to admission.

Case 3.—This 13-month-old white female was admitted to the University Hospital for therapy of a generalized convulsion which followed a seven- to ten-day illness characterized by fever and progressive lethargy and irritability. A lumbar puncture on admission was normal except for the glucose value of 29 mg%. A simultaneous blood glucose value was 14 mg%. The initial serum salicylate level was 64 mg%. She had received an undetermined quantity of aspirin during this illness. Conservative management of her hypoglycemia and salicylism was associated with an uncomplicated recovery. During a 12-hour fast performed seven days after admission, the patient remained asymptomatic with normal blood glucose values.

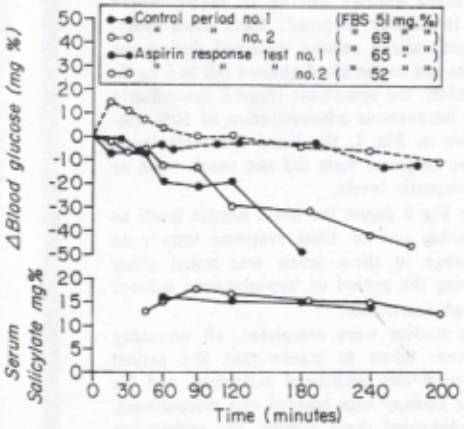

Fig 1.—Aspirin-response tests: Blood glucose by method of O'Brien and Ibbott[6]; serum salicylate by method of Trinder.[7]

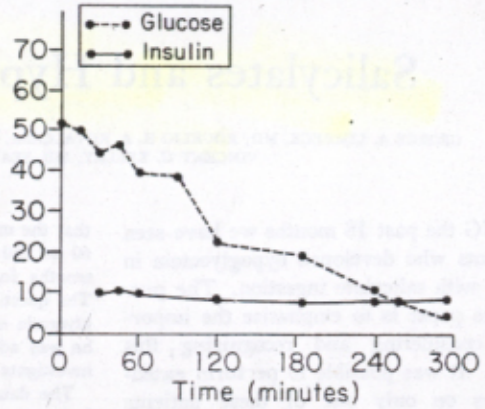

Fig 2.—Effect of salicylate on blood insulin level: Blood insulin by method of Samols and Bilkus.[1] Blood insulin is measured by microunits per milliliter, blood glucose by milligrams percent.

Comment

Hypoglycemic symptomatology in children receiving salicylates has not been reported frequently in the English literature. In 1960, Mortimer and Lepow[3] 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 salicylate in experimental animals with hypoglycemia and a diminished hyperglycemic response to epinephrine. Barnett et al[4] demonstrated hypoglycemia during the course of therapy for acute salicylate intoxication in one patient, although the pretherapy 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 hypoglycemic blood levels and symptoms during these tests were caused by the administration of a subtoxic dose 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 hypoglycemic 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.[5] 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 tricarboxcylic acid cycle, resulting in glycogen depletion 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 salicylate 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, 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 imply. Awareness of this association will aid in the recognition of hypoglycemia in those patients in whom it does occur. Since the symptomatology of salicylism 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.

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.

A portion of this work was conducted through the Clinical Research Center Facility of the University of Washington supported by the National Institutes of Health (grant FR-37). It was supported in part by a training grant in Pediatric Endocrinology and Metabolic Disease (National Institute of Arthritis and Metabolic Diseases training grant No. 2T1-AM-5190).

This work was done during the tenure of a traineeship in Pediatric Endocrinology and Metabolic Disease, National Institute of Arthritis and Metabolic Diseases training grant No. 2T1-AM-5190 (Dr. Limbeck and Dr. Ruvalcaba).

Generic and Trade Names of Drugs

Hydrocortisone—Cortef, Cortifan, Cortril, Hycortole, Hydrocortone.

REFERENCES

1. Samols, E., and Bilkus, D.: Unpublished modification of the method of Yalow, R. S., and Berson, S. A.: Immunoassay of Endogenous Plasma Insulin in Man, J Clin Invest 39:1157, 1960.

2. Done, A. K.: Salicylate Intoxication: Significance of Measurements of Salicylate in Blood in Cases of Acute Ingestion, Pediatrics 26:800, 1960.

3. Mortimer, E. A., Jr., and Lepow, M. L.: Varicella and Hypoglycemia Possibly Due to Salicylates, Amer J Dis Child 103:91, 1962.

4. Barnett, H. L., et al: Salicylate Intoxication in Infants and Children, J Pediat 21:214, 1942.

5. Smith, M. J. H.: Salicylates: International Symposium, London: J. & A. Churchill, Ltd., 1963, pp. 47-54.

6. O'Brien, D., and Ibbott, F. A.: Laboratory Manual of Pediatric Micro- and Ultramicro-Biochemical Techniques, New York: Harper & Row Publishers, Inc., 1962, p 134.

7. Trinder, P.: Rapid Determination of Salicylate in Biological Fluids, Biochem J 57:301, 1954.