Combined Raw Cornstarch and Nifedipine as an Additional Treatment in Persistent Hyperinsulinemic Hypoglycemia of Infancy

CHITTIWAT SUPRASONGSIN, M.D.*,
PAT MAHACHOKLERTWATTANA, M.D.**,
UMAPORN SUTHUTVORAVUT, M.D.**,
CHAWALIT PREEYASOMBAT, M.D.**

Abstract

This study reports the result of treatment with the combination of raw cornstarch and nifedipine in two infants affected with hyperinsulinemic hypoglycemia of variable severity. The first infant developed hypoglycemia during early neonatal period and required subtotal pancreatectomy. She still developed hypoglycemia after her second operation. The second infant developed hypoglycemia at the age of 7 months. Raw cornstarch and nifedipine efficiently normalized both infants' blood glucose levels. Although they still need frequent feedings, no hypoglycemic episode was reported except when they were sick. Their growth and development were markedly improved after initiation of treatment.

Key word : Persistent Hyperinsulinemic Hypoglycemia of Infancy, Raw Cornstarch, Nifedipine, Treatment

Persistent hyperinsulinemic hypoglycemia of infancy (PHHI), which is commonly called nesidioblastosis, is one of the most common causes of persistent hypoglycemia in infants[1]. Although the diagnosis is straightforward by demonstrating an inappropriate increase in plasma insulin levels during hypoglycemia, the cause of disease is still uncertain and controversial.

The histological features of PHHI are also present in infants dying from other conditions not associated with hyperinsulinemic hypoglycemia[2]. Recent molecular genetics demonstrated that familial hyperinsulinemic hypoglycemia of infancy is associated in several families with mutations in the second nucleotide-binding domain of sulfonylurea receptor (SUR)[3]. The mechanism of this defect, a putative increase in the ability of ATP to close K_{ATP} channels, suggests that the ß-cells would be chronically depolarized and therefore insulin hypersecretory. However, the genetic causation may be heterogeneous. Mutations in the glucokinase gene[4] and in the inwardly rectifying potassium channel gene Kir 6.2 have also been identified[5].

* Research Center,
** Department of Pediatrics, Faculty of Medicine, Ramathibodi Hospital, Mahidol University, Bangkok 10400, Thailand.

Treatment options of PHHI include medical and surgical management. Medical treatment consists of the infusion of glucose, the administration of drugs to control insulin secretion, and frequent carbohydrate-rich feedings. Diazoxide and octreotide are the first line medications that are generally given to treat PHHI[6,7]. Unfortunately, these medications are not generally available in Thailand. Cornstarch which is used to treat patients with glycogen storage disease type I was also successfully used to treat patients suffering from PHHI [8]. Recently, nifedipine, a calcium channel blocker was administrated in one patient with promising results[9].

In this article, we report two infants with recurrent hypoglycemia who were suffering from hyperinsulinism and were successfully treated with combination of raw cornstarch and nifedipine at Ramathibodi Hospital.

METHODS

Glucose was measured by the glucose oxidase method with glucose analyzer (Beckman Instruments Inc., Fullerton, CA). Insulin levels were determined by radioimmuno-assay (DPC, Los Angeles, CA).

CASE REPORTS

The 2 patients studied were 4 weeks and 7 months old. Both suffered from persistent hypoglycemia and had documented inappropriately high insulin secretion.

Patient 1

The patient was admitted with hypoglycemic seizures at the age of 4 weeks. Her blood glucose was 25 mg/dl. Despite intravenous glucose infusion (10-15 mg/kg/min), she continued to have intermittent hypoglycemia. Seventeen days after her admission, she underwent subtotal pancreatectomy of 85 per cent. Pathological findings were compatible with the diagnosis of nesidioblastosis. However, she developed hypoglycemic seizures again after her first operation. The second operation of 95 per cent pancreatectomy was then performed 2 months after her initial one. However, she was still unable to maintain euglycemia and required additional medical treatments. Since diazoxide and octreotide were not available at that time, frequent feeding and hydrocortisone were selected as choices of treatment. Then, hydrocortisone was gradually tapered off. She occasionally developed hypoglycemia and was readmitted to Ramathibodi Hospital at the age of 14 months after cessation of hydrocortisone for 1 month. Due to a risk for the third operation, raw cornstarch and dextrin were considered as choices of treatment. To evaluate whether raw cornstarch or dextrin could maintain her blood glucose levels, careful steps of raw cornstarch and dextrin tolerance tests were separately performed in the patient 2 weeks apart. Raw cornstarch or Maltodextrin® 100 (Grain Processing Co., Muscatine, IW) were prepared as suspension in water at room temperature with a weight to volume ratio of 1:2[8]. These suspensions were given at a dose of 1.75 g/kg body weight intragastrically 3-4 hours after fasting. Blood samples were obtained hourly to determine glucose and insulin levels as shown in Table 1. Dextrin raised blood glucose up to 204.9 mg/dl within an hour with a high level of insulin (35.3 μU/ml). At the end of the fourth hour, she developed hypoglycemia with the blood glucose of 39 mg/dl and the test was immediately terminated. Raw cornstarch in the other hand could maintain normoglycemia in a longer period, with-

Table 1. Blood glucose concentrations and insulin levels during raw cornstarch and dextrin tolerance tests.

		Time (hour)								
		-1	0	1	2	3	4	5	6	7
Raw cornstarch (1.75 g/kg)	Glucose (mg/dl)	68.6	51.4	78.5	112.2	98.9	64.4	73.4	58.7	57.3
	Insulin (μU/ml)	4.3	3.3	2.9	3.5	2.1	3.5	3.6	0.9	2.6
Dextrin (1.75 g/kg)	Glucose (mg/dl)	71.4	38.7	204.9	123.4	59.6	39			
	Insulin (μU/ml)	2.9	2.2	35.3	5.3	4.3	3.8			

out any evidences of high insulin levels throughout the test. Therefore, raw cornstarch 2 g/kg every 6 hours was selected to treat this patient. However, she still developed mild hypoglycemia during raw cornstarch administration. Nifedipine, a calcium channel blocker, was then introduced on a dose of 0.5 mg/kg/day, three times a day. Blood pressure was monitored and revealed stable during nifedipine administration. Finally, the patient received the combination of nifedipine of 0.5 mg/kg/day every 8 hours and raw cornstarch of 2 g/kg every 6 hours as home treatment. During eight years of follow-up, she was in good health and had no further hypoglycemia, except when she was ill.

Patient 2

The patient was an uneventfully first born child with birth weight of 3,050 g who developed seizures at the age of 7 months. He was treated with anticonvulsive drugs. He was found to have hypoglycemia during seizures by the pediatrician in his hometown and was referred to Ramathibodi Hospital at the age of 1 year and 9 months. Initial investigation revealed insulin levels of 54.4 μU/ml while his blood glucose was 32 mg/dl. Glucose infusion was started immediately (12-15 mg/kg/min) to maintain euglycemia. Raw cornstarch was introduced in the second week of hospitalization at a dose of 2 g/kg/dose every 6 hours. After raw cornstarch therapy, glucose infusion rate was gradually decreased to 5 mg/kg/min to maintain normoglycemia. However, the further declination of intravenous glucose infusion was not able to perform. Nifedipine was introduced a week later at a dose of 0.3 mg/kg/day and slowly increased to 0.7 mg/kg/day three times a day after one week. After giving the combination treatment, intravenous glucose infusion rate was gradually decreased and finally ceased. The patient was discharged home on this combination therapy. Self-monitoring of blood glucose was performed primarily by the parents using glucometers (Miles Inc., Elkhart, NJ). The patient was seen in Pediatric Endocrine Clinic every 1-2 months. He has had no evidence of hypoglycemia or seizures during the follow-up period of 14 months. His growth and development were dramatically improved.

DISCUSSION

PHHI is a rare condition. The management of medical or surgical approach is controversial. Because of the surgical risk and the likelihood of developing diabetes following pancreatectomy[10], raw cornstarch was initially used in treatment which obviously improved glucose levels in both patients. However, raw cornstarch alone did not adequately maintain euglycemia in both patients. A second medication was used based on *in vitro* study demonstrating that the ß-cells of patients with PHHI were constantly depolarized and persistently firing Ca^{2+} action potentials. The action potentials were rapidly and reversibly terminated by exposure to the voltage activated L-type calcium channel blocker verapamil[9]. Nifedipine, a calcium channel blocker, is introduced because it successfully maintains normal blood glucose in the patient[9] and has less adverse effect on myocardial function than verapamil.

An addition of nifedipine was helpful in maintaining normoglycemia in both patients. The combination of nifedipine and cornstarch treatment avoided total pancreatectomy in patient 1 and subtotal pancreatectomy in patient 2. This treatment is well accepted by the parents and patients rather than octreotide, which must be given by multiple subcutaneous injections and diazoxide which commonly results in hypertrichosis. Moreover, both octreotide and diazoxide treatment are much more expensive than raw cornstarch plus nifedipine. Pancreatectomy is even more expensive if the risk of late diabetes is taken into consideration. However, in Thailand where octreotide and diazoxide are not generally available, subtotal pancreatectomy is inevitably a treatment of choice in severe cases.

Regardless of any treatment given, the patients continue to require regular clinic visits, occasional hospitalization for acute illness, and periodic home blood glucose monitoring. The short-term side effects of combination of raw cornstarch and nifedipine treatment were relatively mild which include abdominal distension and obesity from raw cornstarch.

The combination of nifedipine and raw cornstarch are useful in preventing postoperative hypoglycemia. In mild case, this combination can successfully maintain euglycemia and avoid unnecessary surgical procedure with late diabetes.

In summary, we demonstrated that raw cornstarch combined with nifedipine can be used effectively as an additional treatment for PHHI in mild cases and in hypoglycemia post pancreatectomy.

(Received for publication on October 15, 1999)

REFERENCES

1. Stanley CA. Hyperinsulinism in infants and children. Pediatr Clin North Am 1997; 44:363-74.
2. Milner RD. Nesidioblastosis unravelled. Arch Dis Child 1996; 74:369-72.
3. Thomas PM, Cote GJ, Wohllk N, et al. Mutations in the sulfonylurea receptor gene in familial persistent hyperinsulinemic hypoglycemia of infancy. Science 1995; 268:426-9.
4. Glaser B, Kesavan P, Heyman M, et al. Familial hyperinsulinism caused by an activating glucokinase mutation. N Engl J Med 1998; 338:226-30.
5. Thomas PM, Wohllk N, Huang E, et al. Inactivation of the first nucleotide-binding fold of the sulfonylurea receptor, and familial persistent hyperinsulinemic hypoglycemia of infancy. Am J Hum Genet 1996; 59:510-8.
6. Horev Z, Ipp M, Levey P, Daneman D. Familial hyperinsulinism: successful conservative management. J Pediatr 1991; 119:717-20.
7. Glaser B, Hirsch H, Landau H. Persistent hyperinsulinemic hypoglycemia of infancy: long-term octreotide treatment without pancreatectomy. J Pediatr 1993; 123:644-50.
8. Boneh A, Landau H, Abramovitch N. Raw cornstarch as an additional therapy in nesidioblastosis. Am J Clin Nutr 1988; 47:1001-3.
9. Lindley KJ, Dunne MJ, Kane C, et al. Ionic control of beta cell function in nesidioblastosis. A possible therapeutic role for calcium channel blockade. Arch Dis Child 1996; 74:373-8.
10. Leibowitz G, Glaser B, Higazi AA, Salameh M, Cerasi E, Landau H. Hyperinsulinemic hypoglycemia of infancy (nesidioblastosis) in clinical remission: high incidence of diabetes mellitus and persistent beta-cell dysfunction at long-term follow-up. J Clin Endocrinol Metab 1995; 80:386-92.

การใช้แป้งข้าวโพดดิบร่วมกับยานิฟีดิพีนในการรักษาภาวะน้ำตาลในเลือดต่ำในทารกที่มีอินสุลินสูง

จิตติวัฒน์ สุประสงค์สิน, พ.บ., อุมาพร สุทัศน์วรวุฒิ, พ.บ.**, พัฒน์ มหาโชคเลิศวัฒนา, พ.บ.**, ชวลิต ปรียาสมบัติ, พ.บ.***

ได้รายงานการใช้แป้งข้าวโพดดิบร่วมกับยา nifedipine ในผู้ป่วย 2 ราย ที่มีภาวะอินสุลินในเลือดสูงในระดับความรุนแรงที่แตกต่างกัน โดยผู้ป่วยคนแรกมีอาการน้ำตาลในเลือดต่ำตั้งแต่แรกเกิดจำเป็นต้องรับการผ่าตัด subtotal pancreatectomy หลังผ่าตัดผู้ป่วยยังมีระดับน้ำตาลในเลือดต่ำจนต้องได้รับการผ่าตัดอีกครั้ง ส่วนผู้ป่วยรายที่ 2 มีอาการน้ำตาลในเลือดต่ำเมื่ออายุ 7 เดือน ผู้ป่วยทั้งสองรายได้รับการรักษาต่อด้วยแป้งข้าวโพดดิบร่วมกับยา nifedipine ซึ่งพบว่าสามารถรักษาระดับน้ำตาลให้อยู่ในเกณฑ์ปกติได้ แต่ก็ยังคงต้องให้อาหารค่อนข้างบ่อย โดยไม่มีอาการน้ำตาลในเลือดต่ำยกเว้นถ้ามีอาการเจ็บป่วย ผู้ป่วยมีการพัฒนาการดีขึ้นอย่างเห็นได้ชัดหลังการรักษา และมีการเจริญเติบโตอยู่ในเกณฑ์ที่น่าพอใจ

คำสำคัญ : ภาวะอินสุลินในเลือดสูงในทารก, แป้งข้าวโพดดิบ, นิฟีดิพีน, การรักษา

* สำนักงานวิจัย,

** ภาควิชากุมารเวชศาสตร์, คณะแพทยศาสตร์โรงพยาบาลรามาธิบดี, มหาวิทยาลัยมหิดล, กรุงเทพ ฯ 10400