Pediatr Nephrol (1997) 11: 625–627

Pediatric Nephrology

Brief report

Mizoribine in steroid-dependent nephrotic syndrome of childhood

Takashi Hamasaki, Mikio Mori, Yoshihisa Kinoshita, Tetsuya Saeki, and Takashi Sakano

Department of Pediatrics, Hiroshima Prefectural Hospital, 1-5-54, Ujinakanda, Minami-ku, Hiroshima 734, Japan

Received September 20, 1996; received in revised form and accepted April 24, 1997

Abstract. We evaluated a 1-year course of a newly developed immunosuppressant, mizoribine (at a dosage of 3 mg/kg body weight per day), in nine children with steroid-dependent nephrotic syndrome. Steroid treatment could be discontinued in two patients and the maintenance dosage of steroid could be reduced to less than half of that given before mizoribine therapy in a third. There were no beneficial effects in the remaining six patients. No adverse effects of mizoribine were observed during the course of therapy.

Key words: Mizoribine – Steroid-dependent nephrotic syndrome

Introduction

Most patients with minimal change nephrotic syndrome in childhood respond to steroid therapy. However, some responders have frequent relapses or are steroid dependent [1]. One of the serious problems in these patients is toxicity from continous steroid therapy. Immunosuppressants, such as cyclophosphamide and chlorambucil, often used to induce longer remission have not been satisfactory in steroid-dependent patients [2, 3]. Mizoribine, a newly developed immunosuppressant, inhibits purine nucleoside synthesis [4]. The purpose of this study was to evaluate the efficacy and safety of mizoribine therapy in children with steroid-dependent nephrotic syndrome.

Patients and methods

Nine children (6 males, 3 females) with steroid-dependent nephrotic syndrome were enrolled in the study. The definitions of nephrotic syndrome, remission, and relapse are those used by the International Study of Kidney Disease in Children [5]. Steroid dependence was defined as recurrence of proteinuria when the dose of prednisolone was reduced or within 2 weeks of discontinuation of therapy. The initial episode and first relapse were usually treated with 60 mg/m^2 per day (total dose not more than 60 mg/day) prednisolone for 4 weeks, followed by 40 mg/m^2 per day for 2 weeks, 30 mg/m^2 per day for 2 weeks, then alternate-day prednisolone with 60 mg/m^2 given as a single dose in the morning of every other day for 2 weeks, with the dosage being decreased by 10 mg/m^2 every 2 weeks. At each subsequent relapse, patients were generally treated with 60 mg/m^2 or less per day for 4 weeks, followed by alternate-day tapering, according to their previous response to prednisolone, the dose of prednisolone at relapse, and the clinical course before relapse. Patients who had received immunosuppressive agents within the last 6 months were excluded from the study. Clinical features of the nine patients with steroid-dependent nephrotic syndrome are shown in Table 1. All patients had normal renal function during their clinical course. Renal biopsy was performed in three patients and documented minimal change disease. The other patients were thought to have minimal change nephrotic syndrome based on their clinical findings and response to steroid therapy [6].

Oral mizoribine was started when the patient was in remission and was given at a dosage of 3 mg/kg body weight per day (not exceeding 150 mg/day) in three divided daily doses with maintenance doses of prednisolone. The dosage of prednisolone was then gradually reduced. When relapse occurred during mizoribine therapy, patients were treated with prednisolone in the same manner as before mizoribine therapy and mizoribine was continued for a year. Mizoribine was discontinued after a year. Clinical evaluation and laboratory examination of mizoribine toxicity were performed every 2–4 weeks. Regular laboratory examination of blood and urine consisted of complete blood count, blood urea nitrogen, serum creatinine, uric acid, sodium, potassium, chloride, calcium, phosphate, serum β_2-microglobulin, total protein, albumin, liver function, routine urinalysis, and urinary enzymes such as *N*-acetyl-β-glucosaminidase and β_2-microglobulin. Trough and peak blood levels of mizoribine were measured at 3, 6, 9, and 12 months during mizoribine therapy, according to the method reported previously [7]. Informed consent was obtained from all guardians and patients before mizoribine therapy.

Results

All nine patients completed the trial; three were considered responders to mizoribine. As shown in Table 1, prednisolone was discontinued after starting mizoribine therapy in

Correspondence to: T. Hamasaki

Table 1. Clinical features of the nine children with steroid-dependent nephrotic syndrome

Patient	Sex	Age at onset (years)	Duration of illness before MZB therapy (months)	Age MZB started (years)	Relapses (times)	Mean interval between relapses (months)	Prior therapy	Renal bioopsy	Observation period after MZB therapy (months)	Relapses after MZB therapy (times)	Mean interval between relapses (months)	Effect of MZB therapy
1	M	6	72	12	9	8	Prd Cpm	–	24	0		Withdrawal of Prd
2	F	3	33	6	5	6.4	Prd Cpm	–	20	0		Withdrawal of Prd
3	M	6	94	14	5	19	Prd Cpm	–	24	0		Reduction of Prd[a]
4	M	3	54	7.5	5	10.8	Prd Mps Cpm	MC	27	1	27	(–)
5	M	5	109	14	12	9	Prd Cpm	–	32	3	11	(–)
6	M	4	108	13	11	10	Prd Cpm	–	32	3	11	(–)
7	F	6	131	17	25	5	Prd Cpm	MC	13	4	3	(–)
8	F	2	30	4.5	5	6	Prd Cpm Ggl	–	21	4	5	(–)
9	M	8	100	16	17	6	Prd Cpm	MC	24	4	6	(–)

MZB, Mizoribine; Prd, prednisolone; Cpm, cyclophosphamide; Mps, pulse methylprednisolone therapy; Ggl, high-dose gamma globulin therapy; MC, minimal change
[a] Reduction of Prd was defined as reduction of the dosage of Prd to less than half of that administered before MZB therapy

Table 2. Mean blood levels (μg/ml) of MZB in children with steroid-dependent nephrotic syndrome[a]

	3 responding children		6 non-responding children	
Time (months)	Trough	Peak	Trough	Peak
3	0.28 ± 0.07	0.52 ± 0.20	0.14 ± 0.19	0.40 ± 0.38
6	0.33 ± 0.26	0.55 ± 0.13	0.13 ± 0.09	0.31 ± 0.22
9	0.07 ± 0.09	0.46 ± 0.27	0.10 ± 0.14	0.22 ± 0.15
12	0.16 ± 0.15	0.44 ± 0.07	0.21 ± 0.36	0.51 ± 0.32

$P > 0.05$ when comparing responding patients with non-responding patients at each interval
[a] Mean ± SD

two children; one patient at 7 months and the other at 11 months. These patients remained in remission during the observation period (24 and 20 months, respectively). In the third patient, the dosage of prednisolone could be decreased after 1 year of therapy to 5 mg/48 h, which was less than half of the dosage administered before mizoribine therapy; relapse did not occur during the observation period. In six unresponsive patients, the difference in the rate of relapse and total dosage of prednisolone before and after mizoribine therapy was not significant. Furthermore, there was no statistically significant difference in the duration of illness and the number of relapses before mizoribine therapy between the three responders and the six non-responders.

Peak and trough blood levels of mizoribine measured at 3, 6, 9, and 12 months during therapy are shown in Table 2. Mean peak values of the three responding patients and the six non-responding patients were 0.52 μg/ml and 0.40 μg/ml at 3 months, 0.55 μg/ml and 0.31 μg/ml at 6 months, 0.46 μg/ml and 0.22 μg/ml at 9 months, and 0.44 μg/ml and 0.51 μg/ml at 12 months, respectively. At 3, 6, and 9 months, mean peak blood levels of mizoribine appeared higher in responding patients. However, there were statistically no significant differences between blood levels (peak and trough) of the three responding and six non-responding patients. None of our patients had indications of mizoribine toxicity, such as leukopenia, gastrointestinal symptoms, alopecia, hepatotoxicity, and nephrotoxicity, as assessed by regular examination.

Discussion

Minimal change nephrotic syndrome in childhood is generally a benign disease with a good prognosis. However, steroid toxicity remains a major problem for children with steroid-dependent nephrotic syndrome and is difficult to manage. The effectiveness of alkylating agents, such as cyclophosphamide and chlorambucil, in steroid-dependent nephrotic syndrome is less than optimum and the use of these drugs is restricted by their potential side effects, including gonadal toxicity [2, 3]. The steroid-sparing effect of mizoribine that was observed in three of our patients has been reported previously [8]. Although the remaining six patients did not show comparable benefits, this may relate to the doses of mizoribine used. Unfortunately, we were

unable to determine effective blood levels of mizoribine and chose a conservative dose of 3 mg/kg body weight per day. This dose resulted in no short-term adverse effects of mizoribine. Whether higher doses of the drug would be more effective and free from side effects or whether long-term side effects of mizoribine will develop remains to be determined.

Recently, the use of cyclosporin A in steroid-dependent nephrotic syndrome has been reported [9, 10]. However, long-term cyclosporin A treatment is necessary to maintain remission, and relapse often occurs soon after cessation of cyclosporin A treatment. Furthermore, it is well known that the most serious toxic effect of cyclosporin A is nephrotoxicity, including tubulointerstitial damage which may arise in the absence of any signs of renal functional impairment [10]. Although the efficacy of mizoribine was restricted in our patients with steroid-dependent nephrotic syndrome, mizoribine may prove to be a suitable alternative to alkylating agents or cyclosporin A in selected nephrotic children who prove refractory to currently used drugs or who develop severe side effects from prolonged use of steroids.

References

1. Brodehl J (1991) Steroid and cytotoxic drugs in the treatment of minimal change nephrotic syndrome. In: Hatano M (ed) Nephrology, vol II, Springer, Berlin Heidelberg New York, pp 1458
2. Garin EH, Pryor ND, Fennell RS, Richard GA (1978) Pattern of response to prednisone in idiopathic, minimal lesion nephrotic syndrome as a criterion in selecting patients for cyclophosphamide therapy. J Pediatr 92: 304–308
3. Arbeitsgemeinschaft für Pädiatrische Nephrologie (1982) Effect of cytotoxic drugs in frequently relapsing nephrotic syndrome with and without steroid dependence. N Engl J Med 306: 451–454
4. Mizuno K, Tsujino M, Takeda M, Hayashi M, Atsumi K, Asano K, Matsuda T (1974) Studies on bredinin. I. Isolation, characterization and biological properties. J Antibiot (Tokyo) 27: 775–782
5. International Study of Kidney Disease in Children (1982) Early identification of frequent relapsers among children with minimal change nephrotic syndrome. J Pediatr 101: 514–518
6. Webb NJA, Lewis MA, Iqbal J, Smart PJ, Lendon M, Postlethwaite RJ (1996) Childhood steroid-sensitive nephrotic syndrome: does the histology matter? Am J Kidney Dis 27: 484–488
7. Hosotsubo H, Takahara S, Taenaka N (1988) Simplified high-performance liquid chromatographic method for determination of mizoribine in human serum. J Chromatogr 432: 340–345
8. Igarashi Y, Moro Y, Kondo Y, Inoue CN (1994) Steroid-sparing effect of mizoribine in long-term nephrotic syndrome of children. Pediatr Nephrol 8: 396–397
9. Melocoton TL, Kamil ES, Cohen AH, Fine RN (1991) Long-term cyclosporine A treatment of steroid-resistant and steroid-dependent nephrotic syndrome. Am J Kidney Dis 18: 583–588
10. Niaudet P, Broyer M, Habib R (1991) Serial renal biopsies in children with idiopathic nephrosis receiving cyclosporin. Contrib Nephrol 114: 78–83

Literature abstract

Kidney Int (1997) 51: 777–784

Circulating luteinizing hormone receptor inhibitor(s) in boys with chronic renal failure

Leo Dunkel, Taneli Raivio, Jarmo Laine, and Christer Holmberg

Patients with chronic renal failure frequently have hypogonadism. To elucidate the molecular mechanisms involved, we tested the ability of serum from these patients to inhibit recombinant human luteinizing hormone receptors. Using a cell line expressing functional human luteinizing hormone receptors, we found that adenosine 3′,5′-monophosphate (cAMP) production was markedly inhibited by sera from the patients, but not by sera from healthy subjects. Inhibition of cAMP production was associated with inhibition of ^{125}I-human chorionic gonadotropin binding. Inhibition of LH receptors by sera from patients correlated with the glomerular filtration rate and after renal allograft transplantation, decreased. Fractionation of serum samples indicated the receptor-inhibiting activity in proteins of molecular weights from 30,000 to 60,000 Daltons. When characterized and purified, the factor responsible may well be a new LH receptor antagonist of clinical significance.