Comparative study of prednisolone alone and prednisolone plus fusidic acid in the treatment of children with steroid-responsive nephrotic syndrome

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Summary. *Background. There are several reports in the literature indicating that fusidic acid owns functions similar to those of cyclosporin. As cyclosporin has effectively been used in frequently relapsing steroid-responsive nephrotic syndrome we carried out this study to determine whether fusidic acid used along with prednisolone diminishes rate of steroid-responsive nephrotic syndrome relapses in children.*

Patients and methods. The patients were randomly allocated to receive either prednisolone alone or prednisolone plus fusidic acid for two months in standard doses. In the cases of relapses the treatment was changed to the comparative treatment method. Altogether 18 children (12 boys and 6 girls) aged 1.3 to 13.2 years entered the study. Thirteen of them were treated by either method on different occasions, four patients were treated with prednisolone only, and one child was treated with prednisolone plus fusidic acid only. Thus, there were 17 evaluable treatment courses with prednisolone alone and 14 courses with prednisolone plus fusidic acid. The patients were followed-up as long as the remission lasted.

Results. There was prompt and complete response under the influence of both treatment methods. However, relapses occurred in all the patients irrespective of the mode of treatment. Mean duration of remissions did not differ significantly between the study groups (17.8±20.4 weeks in the prednisolone group and 18.3±23.9 weeks in the prednisolone plus fusidic acid group; $p>0.05$). There were no statistically significant differences in laboratory parameters reflecting therapeutic efficacy in the comparative treatment groups, too.

Conclusion. Thus, it was not revealed any remission-sustaining efficacy of fusidic acid used in standard doses for two months along with prednisolone in children with frequently relapsing steroid-responsive nephrotic syndrome.

Introduction

Idiopathic nephrotic syndrome (NS) morphologically presenting itself most often as minimal change nephropathy is usually treated with steroids. The treatment leads to complete clinical and laboratory remission in more than 75% of the patients (1). However, only in 15–20% of the steroid-responsive patients the remissions are permanent or long lasting. A great majority of the patients experience relapses of the disease (2) and in 25–30% of them recurrences are close-spaced.

Several agents have been used to prevent frequent relapses and to avoid steroid toxicity caused by repeated treatment with glucocorticoids (GC). Cytotoxic agents and cyclosporin (CS) are shown to be effective in diminishing frequency of relapses and prolonging remissions (3–5). Unfortunately, even after a conventional therapy with either cytotoxic agents or cyclosporin frequency of relapses remains in order of 30–70% (5, 6). Prolonging courses of the treatment could increase remission-sustaining efficacy of these agents; however, this increases also mutagenic and carcinogenic potential of cytotoxic agents and nephrotoxicity of cyclosporin (7–9).

Recently it has been stated that a steroid antibiotic, fusidic acid (FA), possesses immunosuppressive activities strikingly resembling those of cyclosporin (10). Immunosuppressive effects of FA have been confir-

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med clinically in patients with some immunologically mediated diseases (11, 12). FA appears to interfere with several of the early processes involved in T-lymphocyte activation (10). Just the NS is supposed to be connected with some abnormalities of T-cell function (5).

Taking this into consideration, we carried out a comparative study of two treatment modalities in children with steroid-responsive nephrotic syndrome (SRNS): 1) prednisolone alone, 2) prednisolone plus fusidic acid.

Patients and methods

Children aged 1 to 15 years and suffering from primary NS were included into the study. The inclusion criteria were as follows:

1) edema,
2) proteinuria (50 mg/kg per day or more) without macrohematuria,
3) hypoproteinemia (50 g/l or less),
4) dysproteinemia (albumin/globulin ratio 1:1 or less),
5) hyperlipidemia (elevated serum levels of cholesterol and/or betalipoproteins),
6) elevated erythrocyte sedimentation rate (ERS, 20 mm/h or more).

For inclusion into the study, it was mandatory presence of proteinuria and at least two more criteria.

Patients' exclusion criteria were as follows:

1) age less than 1 year and over 15 years,
2) hypertension,
3) azotemia (except for elevated serum urea concentration due to hypovolemia),
4) any signs and symptoms of secondary nephrotic syndrome (in systemic diseases, e. g. systemic lupus erythematosus, Schönlein-Henoch purpura, other forms of glomerulonephritis, *etc.*),
5) treatment with GC, cytotoxic and/or immunomodulatory agents at the presentation,
6) contraindications to the treatment with glucocorticoids or fusidic acid.

Patients corresponding to the above inclusion criteria were randomly (by the envelope method) assigned to receive either prednisolone alone (control group) or prednisolone plus fusidic acid (study group).

Patients of the control group were treated with prednisolone in a daily dose of 1.5–2 mg/kg (maximal dose not exceeding 80 mg per day). The initial dose was given until stable disappearance of proteinuria (three consecutive protein-free urine examinations). Then the treatment was continued by the alternate-day regimen for 6 weeks gradually tapering the alternate-day dose. Other drugs (diuretics, vitamins, antimicrobials, except of other immunosuppressive and immunomodulating agents) were allowed during the treatment with prednisolone.

Patients of the study group were treated with prednisolone according to the above scheme plus fusidic acid (Fucidin, Leo Pharmaceutical Products Ltd. A/S, Denmark). The dosage of FA is shown in Table 1.

FA was given immediately after meal. Duration of the treatment was two months. Some other drugs were permitted as in the control group patients (see above).

The patients were treated as in-patients at the Department of Pediatrics, Centre for Pediatrics, Vilnius University Children's Hospital, until improvement of their health status (disappearance of gross edema, decrease of proteinuria) and then as outpatients until the end of the treatment course.

Following examinations were performed before the treatment, after 1 and 2 months of the treatment:
peripheral blood analysis (including differential count),
urinalysis,
total serum protein and its fractions,
serum cholesterol and betalipoproteins,
serum urea and creatinine,
renal ultrasonography,
electrocardiography.

Peripheral blood analyses and urinalyses were also repeated during the treatment at 7 to 14 days intervals. Other analyses were performed or repeated when indicated.

After the end of the treatment the parents were asked to refer to local laboratory for urinalysis once a month and to inform the investigators about the results of the examinations.

The study was carried out from May 1992 through March 1994. The patients were followed-up as long

Table 1. **The dosage of fusidic acid in the study group patients**

Age, years	Single dose, g	Frequency of administration	Daily dose, g
1–4	0.125	4	0.5
5–7	0.25	3	0.75
8–12	0.25	4	1.0
Over 12	0.5	3	1.5

as the remission lasted. When the disease recurred, the patients were switched to another mode of the treatment provided by the study protocol, i. e. to prednisolone plus fusidic acid after the previous course of prednisolone and *vice versa*.

Efficacy of the treatment was evaluated by:

1) time of response, i. e., disappearance of proteinuria,
2) number of patients with full remission during the follow-up period,
3) duration of remissions in patients whom recurred.

The time of response, duration of remissions, differences between results of laboratory examinations before and after treatment within the groups and between the groups were compared by the Wilcoxon test for paired samples or by the Wilcoxon-Mann-Whitney test for unpaired samples, as appropriate. The means and standard deviations (m±SD) of the results of laboratory examinations were calculated as well. In all the calculations p values equal to or less than 0.05 were considered as statistically significant.

Results

Altogether, 18 patients (12 boys and 6 girls) aged 1.3 to 13.2 years entered the study.

Thirteen patients were treated both with prednisolone alone and prednisolone plus fusidic acid, four patients were treated with prednisolone alone, and one patient was treated with prednisolone plus fusidic acid only. Thus, there were 17 evaluable treatment courses with prednisolone alone and 14 courses with prednisolone plus fusidic acid. In all the patients there was prompt and full response to the both treatment modalities (mean time until disappearance of proteinuria under the treatment with prednisolone alone was 13.9±7.4 days, under the treatment with prednisolone plus fusidic acid it was 12.6±6.6; $p>0.05$ for both the paired cases and all the cases). However, NS recurred in all the patients of both groups. Mean duration of remissions in patients treated with prednisolone alone was 17.8±20.4 weeks and in those treated with prednisolone plus fusidic acid it was 18.3±23.9 weeks ($p>0.05$ both for paired cases and for all the cases).

Results of peripheral blood examinations, protein excretion in urine, and blood biochemistry in patients treated with PR alone and PR plus FA and comparison of these results is given in Table 2. As it might be expected, there was a decrease in ESR ($p<0.01$ in both groups), concentrations of cholesterol and betalipoproteins ($p<0.05$ after 1 month in prednisolone group and $p<0.01$ after 2 months in fusidic acid group), increase of total protein ($p<0.05$ after 1 month in both groups), and complete disappearance of proteinuria ($p<0.01$ in both groups). There were also corresponding changes in serum protein fractions (alpha1-, alpha2-, beta- and gamma-globulins) (not shown in the tables). Some decrease in hemoglobin concentration during the treatment with PR plus FA was noted. This and some other differences in laboratory parameters in the two treatment groups are discussed in the "Discussion" section.

In some patients, there were complaints and physical signs that might be attributed to the treatment side effects. Liver enlargement was noted in four of 17 patients treated with PR alone and in two of 14 those treated with PR plus FA; two children treated with PR alone and four treated with PR plus FA complained of abdominal pain. In one patient treated with PR plus FA allergic rash was observed five days before the

Table 2. **Comparison of the changes of laboratory parameters under the treatment with prednisolone alone and prednisolone plus fusidic acid**

Laboratory parameters	At the beginning			After 1 month			After 2 months		
	PR	PR+FA	p	PR	PR+FA	p	PR	PR+FA	p
Hemoglobin (g/l)	131±19	136±11	NS	129±12	129±10	NS	133±11	126±8	NS
Leukocytes (10^9/l)	10.0±3.7	9.3±2.7	NS	12.1±5.2	12.2±5	NS	9.9±3.3	7.6±3.3	0.05
ESR (mm/h)	33±10	32±15	NS	16±11	14±8	NS	10±7	16±15	NS
Total protein (g/l)	54±9	54±8	NS	60±7	63±9	NS	67±3	67±12	NS
Urea (mmol/l)	5.1±1.4	4.9±1.1	NS	6.2±3.8	5.9±1.5	NS	4.6±1.1	5.2±1.4	NS
Creatinine (μmol/l)	39±6	40±16	NS	49±25	30±17	NS	42±10	40±26	NS
Cholesterol (mmol/l)	10.9±4.1	9.1±4.2	NS	6.6±1.8	5.7±1.8	NS	5.4±0.7	5.6±2	NS
β-lipoproteins (g/l)	11.8±4	10.6±5.8	NS	7.5±3.4	6.1±2.6	NS	5.3±1.1	6.4±3.2	NS

Abbreviations and notes: PR – prednisolone; FA – fusidic acid; ESR – erythrocyte sedimentation rate; NS – not significant. The p values were determined by the Wilcoxon-Mann-Whitney test.

end of the two-month treatment course; the treatment was discontinued, but the course was considered to be completed and the case was not excluded from the study. In some patients, activities of alanine aminotransferase and alkaline phosphatase were examined not showing elevations of the activities (the results are not presented in the tables because the number of examinations was too small).

Discussion

Recently it has been shown in an *in vitro* study (10) that fusidic acid exerts immunosuppressive effects resembling those of cyclosporin. The *in vitro* observations have been confirmed clinically in some immunologically mediated diseases (11, 12). Because steroid-responsive nephrotic syndrome is thought to be an immunologically mediated disease (5) and it is successfully treated with cyclosporin (4, 5), it seems to be a sufficient ground for trying to replace the latter by fusidic acid.

However, this comparative study of treatment with prednisolone alone *versus* prednisolone plus fusidic acid in children with steroid-responsive nephrotic syndrome did not show any supplementary effect of the antibiotic. There might be several explanations of the inefficiency of FA in this study. First all, the dose of FA might be too small. It is not determined what dose of FA is necessary to exert its immunosuppressive activity *in vivo*. The dose used by us was approximately the same as recommended for the treatment of bacterial infections. Untoward effects (abdominal pain, liver enlargement, allergic rash) that might be attributed to the use of FA were noted in 6 children of fourteen. However, the antibiotic was used along with prednisolone that could cause abdominal pain and liver enlargement, too. In spite of that, it was our impression that larger doses especially when used for a rather long time (at least for two months) would be intolerable. It was also noted some decrease in hemoglobin concentration (in comparison with that at the beginning of treatment) and leukocyte count (in comparison with the count in patients treated with prednisolone alone). Blood dyscrasias have not been mentioned among possible side effects of fusidic acid (13), although there are anecdotal reports of granulocytopenia due to fusidic acid (14). Thus, a probability of such side effect along with the well-known gastrointestinal and liver disturbances should be taken into account when considering high-dose or long-term use of fusidic acid.

Another reason of the inefficiency of FA might be too short duration of the treatment. It was stated (5, 9) that NS usually relapsed after discontinuation of the treatment with cyclosporin. If immunosuppressive properties of CS and FA are similar, the same sequence of events (*i. e.*, relapses of NS after discontinuation of treatment with FA) should be anticipated, too. Thus, to maintain remissions it would be necessary to continue treatment for a long time (*e. g.*, for six months or more). In such cases, possible side effects and treatment costs should be thoroughly weighed against the anticipated treatment efficacy. Before undertaking such study, it seems to be necessary to learn more about pathogenesis of frequently relapsing steroid-responsive nephrotic syndrome as well as about immunosuppressive properties of fusidic acid.

Conclusion

Fusidic acid used in children with steroid responsive nephrotic syndrome in standard therapeutic doses for two months along with prednisolone has no remission-sustaining effect. Further studies are necessary to elucidate if it is ineffective in steroid-responsive nephrotic syndrome at all or some modifications of treatment scheme are necessary to exert its therapeutic efficacy.

Vaikų steroidams jautraus nefrozinio sindromo gydymo prednizolonu ir prednizolonu kartu su fusido rūgštimi lyginamasis tyrimas

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Raktažodžiai: nefrozinis sindromas, vaikai, prednizolonas, fusido rūgštis.

Santrauka. *Tyrimo tikslas*. Mokslinėje literatūroje yra duomenų, kad fusido rūgštis veikia panašiai kaip ciklosporinas. Kadangi ciklosporinu veiksmingai gydomas dažnai recidyvuojantis steroidams jautrus nefrozinis sindromas, šio darbo tikslas buvo ištirti, ar fusido rūgštis, vartojama kartu su prednizolonu, mažina vaikų steroidams jautraus nefrozinio sindromo recidyvų dažnumą.

Medžiaga ir metodai. Ligoniai atsitiktinės atrankos būdu buvo suskirstyti į gydymo vien prednizolonu ir

prednizolonu su fusido rūgštimi grupes. Gydymo kursų trukmė – du mėnesiai standartinėmis dozėmis. Įvykus recidyvui buvo skiriamas kitas (iš dviejų lyginamųjų) gydymo būdas. Iš viso tirta 18 vaikų (12 berniukų ir 6 mergaitės) nuo 1,3 iki 13,2 metų. Trylika iš jų gydyti ir vienu, ir kitu metodu (įvykus recidyvui po pirmojo gydymo būdo), keturi vaikai gydyti tik prednizolonu, vienas – tik prednizolonu kartu su fusido rūgštimi. Taigi gydymo rezultatus buvo galima vertinti po 17 kursų ir po 14 gydymo prednizolonu kartu su fusido rūgštimi kursų. Ligoniai buvo stebimi tol, kol truko remisija.

Rezultatai. Ir vienu, ir kitu būdu gydytiems ligoniams buvo greita ir visiška remisija. Tačiau visiems ligoniams anksčiau ar vėliau liga recidyvavo. Vidutinė remisijos trukmė nesiskyrė, lyginant pagal gydymo būdą (atitinkamai 17,8±20,4 ir 18,3±23,9 savaitės; $p>0,05$). Taip pat nebuvo statistiškai reikšmingų laboratorinių rodmenų, atspindinčių gydymo veiksmingumą, skirtumo.

Išvada. Šio tyrimo duomenimis, fusido rūgštis, du mėnesius vartojama standartinėmis dozėmis kartu su prednizolonu, nepailgina dažnai recidyvuojančiu steroidams jautriu nefroziniu sindromu sergančių vaikų ligos remisijų ir neapsaugo nuo recidyvų.

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