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CLINICAL TRIAL ON PRM PREPARATIONS IN THE TREATMENT OF PATIENTS SUFFERING FROM URINARY APPARATUS INFECTIONS

SUMMARY

RESEARCH PERIOD: 07.2010 – 12.2010
– Topic: high incidence of Urinary Apparatus infections requires a very efficient treatment.
However, the administration of antibacterial drugs does not solve all these problems, allowing the recurrent way of diseases, not reaching irritator eradication which requires prevention with antimicrobial and other drugs not matching clinical needs.
– Research methods: clinical.
– Patients: 10 in the Main Group (research); 10 in the Experimental Group.
– Diagnosis and main inclusion criteria: Urinary Apparatus infections, patients aged 18-65 years.
– Examined preparations, dosage and administration: GUNA-Kidney – prescribed for 1 week, 10 drops 5 times a day; 2nd-8th week 10 drops 3 times a day. Eubioflor and GUNA-Diur were prescribed at the same posology.

– Duration of treatment: 8 weeks.
– Research criteria: microbial inflammation signs.
Efficiency: treatment efficiency in the Main Group should be higher than in the Experimental Group.
– Safety: if any side effect appears (adverse effects) the research is stopped.
– Statistical methods: analysis of variance (Student).
– Conclusions: limited clinical study on GUNA-Diur, GUNA-Kidney, Eubioflor proved the absence of side effects, good tolerance, efficiency of named preparations for cases with Urinary Apparatus infections.
Efficiency result: 70%.
Safety result: no side effects detected.

KEY WORDS **URINARY APPARATUS INFECTIONS, GUNA-KIDNEY, EUBIOFLOR, GUNA-DIUR, PHYSIOLOGICAL REGULATING MEDICINE, LOW DOSE**

ETHIC ISSUE

This clinical study was conducted according to the "Law of Ukraine On Medications" and the Helsinki Declaration last review.
All patients were provided with the information about the study aim "Informative Patient Letter", and agreed.
During the research process neither conflicts nor participation refusal appeared.

INTRODUCTION

Urinary system infections play a considerable role in the structure of diseases.

This term means the contamination of the Urinary Tract without clarification point of the Urinary Apparatus affected level.
In such infections the microorganisms range varies according to the age, gender, way of infection spread, and disease form.

The highest incidence is shown for Gram-negative flora in 60-70% - *E.coli*; less often – pathogenic *Streptococcus* and *Staphylococcus*; high incidence not only of mono-flora but of associated microorganisms.
Clinical strategy herein is aimed primarily to reduce the microbial-inflammatory process and must be implemented in accordance with toxic preparation properties, efficiency in relation to the most frequent agents of disease, as well as with the preparation ability to create therapeutic concentration in tissues, patient's age, level of renal dysfunction, urinal pH, etc.

– The prominent role in renal and Urinary Apparatus infections treatment provide the medicines of wide action range able to inhibit both Gram-positive and Gram-negative flora.

As a rule, frequently recurrent infections of the Urinary Tract requires the supportive antibacterial therapy.
Constant is the aim on finding the way to rise the efficiency of Urinary Apparatus infection treatment.
Physiological Regulating medicine (PRM) preparations produced by GUNA Laboratories (Italy) – present the innovative conception of *low dose* medicine development.
These preparations are innovative in *low dose* medicine, comprising potentiated **hormones**, **neuropeptides**,

cytokines and **growth factors**.

It was suggested for the complex therapy to use: **Guna-Kidney** – basic remedy for renal diseases treatment possessing also neuroprotective effect; **Eubioflor** – preparation applied for intestinal microflora; Pilosella Compositum (**Guna-Diur**) – preparation of emictory, anti-inflammatory, and antiseptical effects.

Taking into account the high incidence of (chronic aggravations) infection-inflammation renal and Urinary System diseases: **primary** and **secondary pielonephritis**, **cystitis**, **urethritis**.

Urinary System infections (2nd place after acute respiratory viral infection), the development of rising the treatment efficiency strategy is of immediate interest.

TRIAL PLAN

GENERAL PLAN

Open, randomized clinical trial.
Guna-Kidney – a basic preparation for renal diseases treatment, was prescribed for 1 week, 10 drops 5 times a day; 2nd-8th week – 10 drops 3 times a day; same posology for **Eubioflor**, and **Guna-Diur**.
– This trial included **20** patients, divided into 2 Groups: 1st Group – patients treated by complex administration of antibacterial medicines + GUNA *low dose* preparations; 2nd Group – patients treated with antibacterial medicines only (fluoroquinolones, penicillin family antibiotics, nitrofurantoin).

Patients of both Groups were randomized according to age, gender, nosological disease form, level of disease intensity.
– The trial was conducted during 8 weeks in accordance to the patient's state and pathology type, which is enough to evaluate the efficiency.

	week 1		week 2		week 3		week 4		week 5		week 6		week 7		week 8	
	1rp.	2rp.	1 rp.	2rp.	1rp.	2rp.	1rp.	2rp.	1rp.	2rp.к	1rp.	2rp.	1 rp.	2rp.	1rp.	2rp.
Lumbalgia																
Edema																
Dysuria																
Headache, weakness																
Appetite																
Body temperature																
Leucocytosis																
Albumins																
Urine leucocytes																
Albuminuria																
Cylindruria																
Urinary bacterial test																
Fecal path. flora																
Blood pressure																
Ultrasound result																
Relapse																
Side effects																
Treatment tolerability																

TAB. 1
Systematic plan of the clinical trial.

POPULATION SELECTION

– Inclusion criteria
For the preparations efficiency evaluation, both genders were included from 18 to 65 years old.
These patients were suffering from acute (chronic aggravations) infection-inflammation renal and Urinary System diseases: **primary** and **secondary pielonephritis**, **cystitis**, **urethritis**.

Patients inclusion was possible with the patient's written agreement to be enrolled in the clinical study.
Patients were included in Groups by random selection.
Each patient was allowed to participate in the clinical study 1 time only. All the identification information about the patient (name, birth-date, case report, etc.) was registered in the "Personal patient card".

– Exclusion criteria
Contraindications for patient's inclusion in the trial are the following: high sensibility to the preparation components, heavy liver and kidney disorders, pregnancy, heavy circulatory decompensation, pulmonary insufficiency of II-III level, decompensated diabetes, mental disorders, drug and alcohol addiction, other conditions considered as inappropriate,

– Patient's refusal
Patients elimination from the trial or testing. Elimination was provided due to patient's refusal, treatment compliance violation, diagnosis change, other necessary treatments.

THERAPY

Treatment was indicated after diagnosis by means of physical and instrumental examinations, bacterial test on the first day, taking into account Urinary System infections in patients.
– Inclusion was made by random selection.

Patients	Main Group	Experimental Group
Age (years)	48,7 ± 5,4	40,5 ± 3,6 *
Gender m/f %	≈10% / 90%	20% / 80% *

TAB. 2
Groups of patients.

**difference between main and experimental Group is apocryphal.*

EFFICIENCY AND SAFETY

When arrived to the hospital, all patients were examined for evaluation of possible inclusion into the clinical trial, with indicating the anamnesis (allergy in particular), preliminary antibiotics therapy data (for chronic diseases), and its efficiency.

The following data were evaluated and put in documentation: birth-date, gender, body mass, and

- anamnesis *data*
- anamnesis *morbi*
- associated disease and associated therapies
- disease at the beginning
- preliminary treatments
- patient's complains: lumbalgia, dysuria, headache, high temperature,
- objective examination *data*: pulse, blood pressure, topoalgia, Pasternatsky's symptom, emiction frequency, urine amount.
- laboratory examination *data*: general blood and urine tests, urine Nechiporenko's test (in case of light leukocyturia), day's albuminuria, urine bacterial inoculation and antibiogram results, dysbiosis fecal examination results, biochemical blood test (BUN, creatinine, liver tests: GPT, GOT, bilirubin, thymol test); kidney X-ray and ultrasound (studied for diagnosis verification), ECG.

Stated indexes were evaluated before and after treatment (every week) (TAB. 1).

Diagnosis	Main Group*	Experimental Group*
Acute pyelonephritis	2(20%)	3(30%)
Chronic pyelonephritis, aggravation	4(40%)	4(40%)
Acute cystitis	3(30%)	1(10%)
Recurrent cystitis in course with recurrent slice	1(10%)	2(20%)

TAB. 3 **Patients selection according with to the diagnosis.**

**difference between main and experimental Group is apocryphal.*

Symptom	Before treatment				On 10-14 day of treatment				After 8 weeks			
Unwellness	0	1	2	3	0	1	2	3	0	1	2	3
Lumbalgia	0	1	2	3	0	1	2	3	0	1	2	3
Headache	0	1	2	3	0	1	2	3	0	1	2	3
Dysuria	0	1	2	3	0	1	2	3	0	1	2	3
Appetite	0	1	2	3	0	1	2	3	0	1	2	3

TAB. 4 **Clinical efficacy appraisal chart.**

Indexes	Main Group (n=3)		Experimental Group (n=2)	
	Before treatment	After 8 weeks	Before treatment	After 8 weeks
Creatinine	0,23±0,11	0,18±0,12	0,24±0,13	0,23±0,11
Urea	14,8±4,32	11,9±4,1	15,8±2,4	14,9±3,25
GFR	42,21±4,21	48,19±3,45	45,21±3,21	44,12±3,62

TAB. 5 **Creatinine, urea and GFR indexes analysis in patients suffering from CRD of 3rd stage pyelonephritis.**

PATIENTS

From July to December 2010, were examined **20 patients** aged 18-65 years, 3 men, 17 women (TAB. 2).

Every patient suffered from Urinary System infections (acute cystitis, recurrent cystitis, acute pyelonephritis, chronic pyelonephritis aggravation (TAB. 3).

All patients were divided into 2 Groups: 10 patients were given antibacterial preparation + PRM therapy (**Main Group**); 10 patients of **Experimental Group** received only antibacterial preparations: 1 for cystitis lasting 3-5 days, 2 and more – for pyelonephritis lasting 10-14 days depending on the clinical picture.

Among all the included patients in 15 cases the GFR was >60ml/min, corresponding to the normal renal function, and 5 cases with the CRD of 3rd stage with reduced GFR intensity <60ml/min.

EFFICIENCY

General clinic efficiency was evaluated according to objective and subjective indexes dynamics for each patient.

Evaluation of particular symptoms was performed with the help of verbal scale: 0 – not indicated; 1 – low rate; 2 – medium rate; 3 – high rate of medicine efficiency.

Stated data demonstrated that such patients' complains as lumbalgia, dysuria, low/no appetite, asthenia after 2 weeks of treatment were diminished, with further dynamics (TAB. 4).

	1 week		2 week		3 week		4 week		7 week	
	1gr.	2 gr.	1 gr.	2 gr.	1 gr.	2 gr.	1gr.	2 gr.	1 gr.	2 gr.
Lumbalgia in grades	21	22	14	12	7	10	6	9	3	7
Edema	2(20%)	1(10%)	2(20%)	1(10%)	1(10%)	1(10%)	1(10%)	1(10%)	1(10%)	1(10%)
Dysuria in grades	9	8	3	4	1	1	1	1	0	1
Headache, asthenia in grades	18	17	9	9	3	5	4	2	2	2
Appetite in grades	15	18	5	10	6	3	1	1	1	1
Rise of body temperature	6(60%)	7(70%)	2(20%)	3(30%)	2(20%)	2(20%)	2(20%)	2(20%)	1(10%)	1(10%)
Leucocytosis (number of patients)	6(60%)	7(70%)	2(20%)	3(30%)	1(10%)0	2(20%)	1(10%)	1(10%)	1(10%)	1(10%)
Urine leucocytes	10(100%)	10(100%)	4(40%)	5(50%)	2(10%)0	3(30%)	2(20%)	2(20%)	2(20%)	2(20%)
Albuminuria	3(30%)	4(40%)	2(20%)	2(20%)	2(20%)	2(20%)	1(10%)	1(10%)	1(10%)	1(10%)
Cylindruria	6(60%)	7(70%)	2(20%)	3(30%)	1(10%)0	2(20%)	1(10%)	1(10%)	1(10%)	1(10%)
Bacteriuria	10(100%)	10(100%)	4(40%)	5(50%)	2(10%)0	3(30%)	2(20%)	2(20%)	2(20%)	2(20%)
Fecal path. flora	3(30%)	4(40%)	2(20%)	5(50%)	2(20%)	2(20%)	0	2(20%)	0	1(10%)
Blood pressure increase	6(60%)	7(70%)	2(20%)	3(30%)	2(20%)0	2(20%)	2(20%)	2(20%)	2(20%)	2(20%)
Relapse										1(10%)
Side effects	0	2	0	1	0	1	0	0	0	0
Treatment tolerability	100%	100%	100%	90%	100%		100%		100%	

TAB. 6

Clinic-laboratory treatment efficiency test in both Groups.

Particularly interesting are the GFR dynamics in patients of both the Main and the Experimental Group, marking the improvement in CRD (TAB. 5).

Stated *data* demonstrate that such patients' complains as lumbalgia, dysuria, low/no appetite, asthenia after 2 weeks of treatment were diminished, with further dynamics (TAB. 6).

Treatment efficiency evaluation was performed by every patient based on the following criteria: «good», «medium» or «bad» (TAB. 7).

General efficiency evaluation	Main Group	Experimental Group
Good	7(70%)	6(60%)
Medium	3(30%)	3(30%)
Bad		1(10%)

TAB. 7

General clinical efficiency evaluation (patient) based on the dynamics of his/her clinical complains.

Clinical-laboratory efficiency rate was based on the following criteria: improvement, partial positive dynamics, worsening (TAB. 8).

Criteria	Main Group	Experimental Group
Improvement	8(80%)	6(60%)
Partial positive dynamics	2(20%)	3(30%)
Worsening	0	1(10%)

TAB. 8

General clinical-laboratory efficiency rate.

It is important to consider that the bacterial inoculation with sensibility define period takes 5 days that is why antibiotics were prescribed before getting the result. The most frequent (50% cases) were pathogenic ***Escherichia coli*** (30% cases), pathogenic *Streptococcus haemolyticus, Streptococcus faecalis*, less frequent, *Proteus mirabilis, Klebsiella, Staphylococcus aureus, Citrobacter,* and others (20%).

Attention should be paid also to the fact that irritator eradication appeared in 8 patients of the Main Group and in 6 patients of the Experimental Group.

– Positive is the absence of recurrent cases in the Main Group, while in the Experimental Group it has been recorded 1 case of aggravation.

GUNA *low dose* preparations performed the considerable positive impact on renal functional indexes.

Even if these changes are statistically apocryphal as well as in comparison with the Experimental Group – the improvement of such indexes as creatinine, urea and GFR are greatly considerable in the course of CRD.

Not a single patient in the Main Group complained on dysbiosis, meanwhile in 40% of the Experimental Group the administration of fluconazole, for 5 patients - probiotics were needed.

Great attention was paid to patients without gaining the desirable therapeutic effect.
These were 2 patients of the Main Group and 4 patients of the Experimental Group. In fact they all were suffering from the aggravated pyelonephritis in the course of cholecystolithiasis (2 patients), 2 patients – after Urinary Tract surgery, 2 patients had pyelonephritis aggravation in course with cystic disease.
For 1 patient of the Experimental Group negative GFR changes were indicated.

TOLERABILITY AND SAFETY

Tolerability of PRM preparations **Guna-Kidney**, **Eubioflor** and **Guna-Diur** appeared to be good.

During the preparations administration and after the treatment end, patients had no complains about after-taste, feces disorder or other undesirable effects; objectively while conducting clinical, instrumental and laboratory tests no *data* on pathological rate, pulse, blood pressure, ECG changes, as well as changes in general and biochemical blood and urine tests were indicated.

– No case of allergic and other undesirable or negative effects were recorded.

CLINICAL-LABORATORY RESEARCH EVALUATION

On the basis of this limited clinical trial on the administration of GUNA PRM preparations **Guna-Kidney**, **Eubioflor** and **Guna-Diur** *vs* antimicrobial treatment only – we can provide the following conclusions:

– GUNA preparations under this trial by the effect and absence of negative side effects can be prescribed for patients suffering from Urinary System infection to be added to the therapy with antimicrobial drugs. ■

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