Research Result: Pharmacology and Clinical Pharmacology

Research Result: Pharmacology and Clinical Pharmacology 4(1): 27–32
UDC: 615.065+616.053.2
DOI 10.3897/rrpharmacology.4.25252

Research Article Rus

New methods to detect early manifestations of adverse side effects of glucocorticosteroids in children

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Academic editor: *Tatyana Pokrovskaya* ♦ **Received** 1 February 2018 ♦ **Accepted** 19 March 2018 ♦ **Published** 28 March 2018

Citation: Batishcheva GA, Zhdanova OA, Nastausheva TL, Goncharova NY, Chernov YN (2018) New methods to detect early manifestations of adverse side effects of glucocorticosteroids in children. Research Result: Pharmacology and Clinical Pharmacology 4(1): 27–32. https://doi. org/10.3897/rrpharmacology.4.25252

Abstract

Introduction: The article focuses on the early manifestations of adverse side effects in children with nephrotic syndrome receiving glucocorticosteroids. The search for criteria of early side effect manifestations is a real challenge nowadays. The authors developed new diagnostic criteria for early detection of pharmacotherapeutical side effects in children with nephrotic syndrome.

Objective: The aim of the study was to develop integral quantitative diagnostic criteria for early detection of side effects of glucocorticosteroids when treating nephrotic syndrome in children.

Materials and Methods: The study included 58 in-patients, aged 1-18. All the children had been thoroughly examined and their parameters had been investigated: height and body mass by calculating Z-scores (WHO ANTHRO Plus) and body mass index (BMI), a biochemical blood test, a full blood count by studying the total number of leukocytes, the percentage of neutrophils and monocytes in peripheral blood, systolic and diastolic blood pressure.

Results and Discussion: The parameters that changed in the patients with nephrotic syndrome taking corticosteroids are referred to as diagnostic criteria. They included leukocytes, neutrophils and monocytes parameters in the full blood count, blood glucose and amylase level, patients' body mass, BMI, systolic and diastolic arterial pressure. The authors defined the change range of the parameters under study in the children with nephrotic syndrome based on the obtained findings.

Conclusion: The authors conclude that application of the developed indices will make it possible to diagnose early metabolic, cardio-vascular and immunologic changes in patients with nephrotic syndrome taking glucocorticoids and perform their individual pharmacological correction in a timely manner.

Keywords

adverse drug reaction, nephrotic syndrome, glucocorticoids, children

Introduction

The pharmacotherapy applied in treating most diseases is characterised not only by the efficiency of arresting diverse pathologies, but also by developing various adverse side effects (Cliff-Eribo 2016). The more active the drug is in interfering with various pathological body processes, the more serious are the caused side effects. Looking for

early criteria of side effect development is considered to be a real challenge nowadays. The authors investigated new diagnostic criteria for early detection of pharmacotherapeutical side effects in children with nephrotic syndrome.

High doses of glucocorticosteroids which make remission possible in most patients are used in treating nephrotic syndrome in children (Ministry of Healthcare of the Russian Federation 2018, KDIGO 2012). A prolonged corticosteroid therapy can lead to the development of adverse side effects such as arterial hypertension, Cushing's syndrome, glucose intolerance, osteoporosis, gastro-intestinal disorders, leukemoid reactions, increased susceptibility to infectious diseases etc. (Landyshev 2014, Aljebab et al. 2017). Side effects of glucocorticosteroid therapy depend on both a treatment dose and its duration and on a patient's individual susceptibility. They are classified depending on the hormone impact on various body systems – the central nervous system, endocrine system, cardio-vascular system, the gastro-intestinal tract, immunity etc. (Strachunsky and Kozlov 2018). A great number of researchers have assessed the influence of various schemes of glucocorticosteroid therapy on the risk of developing nephrotic syndrome recurrence in children and the frequency of therapeutical side effects; however, no early diagnostic on adverse side effects which would offer the possibility to correct the administered therapy in a timely manner has ever been performed (Hjorten et al. 2016, Obuhkova and Dlin 2014).

Objective: This study was aimed at developing integral quantitative diagnostic criteria for early detection of side effects of glucocorticosteroids administered in the therapy of nephrotic syndrome in children.

Materials and Methods

In 2012-2014, 58 in-patients were examined with nephrotic syndrome, aged 1-18, receiving treatment at Voronezh Regional Clinical Paediatric Hospital № 1. The height and body mass with calculation of the body mass index (BMI) according to the formula had been measured in all the children. Z-scores (WHO ANTHRO Plus) and BMI reference ranges were calculated in the children from birth to 5 years and from 5 to 19 years (WHO 2018). A biochemical blood test was undertaken by studying the glucose and amylase level in blood serum, as well as a full blood count by examining the total number of leukocytes, the percentage of neutrophils and monocytes in peripheral blood. All forms of neutrophil leukocytes detected in children (metamyelocytes, myelocytes, immature, stab, segmented neutrophils) were taken into consideration when calculating a neutrophil percentage.

The children with nephrotic syndrome received a prolonged therapy with high doses of corticosteroids (Hahn et al. 2015, Lombel et al. 2013). Metabolic and clinical parameters in the patients were measured repeatedly at various stages of the disease: at the onset or relapse stage, prior to corticosteroid administration, weekly during their administration, during remission and after the drug withdrawal. Amongst the patients under study, there were children with adverse reactions when treated with corticosteroids.

The priority of the suggested methods was recognised by the patents granted by the Russian Federation (Russian Federation Patent 2 633 591(13) 2017, Russian Federation Patent 2 633 592(13) 2017).

All stages of the study were consistent with legislation of the Russian Federation, international ethical standards and approved by the Ethics Committee of Voronezh State Medical Academy named after N.N. Burdenko.w

Results and Discussion

As a result of the studies conducted, methods were proposed for early detection of side effects of corticosteroids to various types of metabolism and leukocytes of peripheral blood in children with nephrotic syndrome, so that timely pharmacological correction of adverse side effects of corticosteroids could be performed.

To develop diagnostic criteria, the parameters that changed in patients with nephrotic syndrome during corticosteroid therapy were selected. They included leukocytes, neutrophils and monocytes parameters in the full blood count, blood glucose and amylase level, patients' body mass, systolic and diastolic arterial pressure findings. The measurement of the changeable parameters in the patients was carried out repeatedly at various stage of the disease: at the onset or relapse stage, prior to corticosteroid administration, weekly during their administration, during remission and after drug withdrawal. The change range of the parameters under study in the children with nephrotic syndrome was determined based on the obtained findings. The comparison group included 120 healthy children and adolescents, whose parameters under study were also measured. Table 1 contains the example of the obtained change range of the parameters in the healthy children and in the patients with nephrotic syndrome.

A modification coefficient was calculated for each of the defined parameters according to formula (1):

$$M = 30 \text{ x } \frac{Ai - Amin}{Amax - Amin} \quad (1),$$

where M – a modification coefficient of each parameter,

Ai – a value of one of the parameters to study,

Amax and Amin –change limits of the parameters in healthy people and in patients with nephrotic syndrome (Table 1).

With the help of formula (1), the parameters under study are brought to the unified scale from 1 to 30, which makes it possible to differentially assess and compare the deviation scope of the studied values.

The values of segmented neutrophils (Segs), systolic arterial pressure (SAP), diastolic arterial pressure (DAP)

Table 1. Change Range of Parameters Under Study in Healthy Children and in Patients with Nephrotic Syndrome

			Patients with nephrotic syndrome					
	Healthy children		No adverse drug side effects to corticosteroids		Adverse drug effect to corticosteroids		Values of the parameters under study	
Parameters	**Min***	**Max***	**Min***	**Max***	**Min***	**Max***	**Amin****	**Amax****
Leukocytes, $\cdot 10^9$/l	4.0	10.3	3.5	10.5	11.0	31.5	3.5	31.5
Neutrophils, %	21	63	19	62	44	84	19	84
Monocytes, %	2	8	3	7	7	17	2	17

Note: * – minimum and maximum values of the studied parameters obtained when examining children and patients with nephrotic syndrome; ** - change range of the studied parameters.

and heart rate (HR) obtained in the patients were expressed in deviation percent of the mean value of the age norm using formula (2):

$$Ai\ (\%) = \frac{Apat * 50}{Amean} \quad (2),$$

where Ai – a value of one of the investigated parameters,
Apat – a value of the investigated parameter in a patient,
Amean – a mean value for a child of a given age and gender.

Diagnostic indices – index of metabolic reactions (IMR) by formula (3), index of immunological reactions (IIR) by formula (4), index of cardio-vascular reactions (ICR) by formula (5) – were calculated by applying the modification coefficient.

$$IMR = \frac{Mbmi + Mgl + Mam}{3} \quad (3),$$

where IMR – index of metabolic reactions,
Mbmi – a modification coefficient of BMI,
Mgl – a modification coefficient of glucose,
Mam – a modification coefficient of amylase.

$$IIR = \frac{Mleu + Mstab + Msegm + Mmon}{4} \quad (4),$$

where IIR – index of immunological reaction,
Mleu – a modification coefficient of leukocytes,
Mstab – a modification coefficient of stab neutrophils,
Msegm – a modification coefficient of segmented neutrophils,
Mmon – a modification coefficient of monocytes.

$$ICR = \frac{Msyst + Mdiast + Mhr}{3} \quad (5),$$

where ICR – index of cardio-vascular reactions,
Msyst – a modification coefficient of systolic blood pressure,
Mdiast – a modification coefficient of diastolic blood pressure,
Mhr – a modification coefficient of the heart rate.

Reference index values – IIR <12 units, IMR ≤ 14.5, ICR < 14 units - were developed on the basis of the performed studies of the test parameters in the healthy children. If the patient's indices are within these ranges, no pharmacological correction for the adverse side effects of glucocorticosteroids is necessary.

A boy X, aged 6, was examined during a regular check-up prior to school admission. His diagnosis was: healthy. The results of this examination are shown in Table 2 together with the calculated indices.

The calculated integral indices (Table 2) when examining the boy, were IMR – 8.0 units (IMR ≤ 14.5), IIR – 5.6 units (IIR <12), ICR – 9.0 units (ICR < 14), which proved the conclusion about his adequate state of health.

A boy Z, aged 7, was diagnosed with nephrotic syndrome, steroid-sensitive variant. He had been ill for two months, now in a remission period. He had a safe kidney function. He had received a glucocorticoid (prednisolone) therapy, dose 60 mg/m^2 of his body surface, for 6 weeks. The boy was examined before transfer to the alternating treatment period.

The results of this examination are given in Table 3 together with the calculated indices.

The calculated integral indices (Table 3) when examining the boy Z, were IMR – 16.1 units (IMR > 14.5), IIR – 14.8 units (IIR > 12), ICR – 9.5 units (ICR < 14), which testified to the adverse side effects of glucocorticoids on the metabolism and leukogram and demanded administration of pharmacological correction and dynamic control of the above-mentioned parameters during the ongoing corticosteroid therapy.

Conclusions

Assessment of the influence of various schemes of corticosteroid therapy on the development of nephrotic syndrome relapses in children and frequency of detection of adverse side effects is highlighted in the Cochrane review (Hahn et al. 2015). However, adverse reactions in the studies included in this review were assessed only regarding various therapeutical schemes; there have been no specific studies to examine side effects of corticosteroid therapy in children with nephrotic syndrome (Ishikura 2015). There has been no specification of various groups of adverse effects depending on the impact of corticosteroids on various body systems.

There are some recommendations known nowadays on monitoring children with nephrotic syndrome receiving corticosteroid therapy (Lombel et al. 2013). They include a list of necessary clinic, laboratory and instrumental parameters and their test frequency. However, no specific groups of parameters indicating the influence of corticosteroids on various body systems (metabolic, immunologic and others) are identified; neither are there all the metabolic parameters that can change when taking

Table 2. Examination Results of Boy X

Group of findings	Parameters*	Modification coefficients of the parameters**	Integral indices***
Metabolic findings	Height – 120 cm, Body mass – 22 kg, BMI – 15.3 z-score BMI = -0.15	Mbmi = 13.2	IMR = 8.0
	Glucose = 4.2 mmol/L	Mgluc = 5.7	
	Amylase = 42 mg%	Mam = 5.1	
Full blood test findings	leukocytes = $4.7 \cdot 10^9$/л	Mleuk = 2.9	IIR = 5.6
	Stab neutroph. = 1 %	Mstab = 2.0	
	Segm. neutroph. – 44% Segm. neutroph. = 47.3% of the norm	Msegm = 13.8	
	Monocytes = 5%	Mmon = 3.9	
Cardio-vascular system	Syst. BP – 95 mm Hg. Syst. BP = 46.6% of the norm	Msyst. = 8.6	ICR = 9.0
	Diast. BP – 65 mm Hg Diast. = 49.2% of the norm	Mdias. = 9.7	
	HR – 90 beat per min HR = 46.4% of the norm	Mhh = 8.6	

Note: * – BMI – body mass index, z-score – body mass calculated in WHO ANTHRO Plus, stab neutroph. – stab neutrophils, segm. neutroph. – segmented neutrophils, syst. BP – systolic blood pressure, diast. BP – diastolic blood pressure, HR – heart rate;
** – Mbmi, Mgluc, Mam, Mleuk, Mstab, Msegm, Mmon, Msyst, Mdias, Mhr – modification coefficients of body mass index, glucose, amylase, leukocytes, stab neutrophils, segmented neutrophils, monocytes, systolic blood pressure, diastolic blood pressure, heart rate respectively;
*** – IMR – index of metabolic reactions, IIR – index of immunological reactions, ICR – index of cardio-vascular reactions.

Table 3. Examination Results of Boy Z

Group of findings	Parameters*	Modification coefficients of the parameters **	Integral indices***
Metabolic findings	Height - 129 cm, Body mass – 35 kg, BMI – 21.0 z-score BMI = 2.48	Mbmi = 20.4	IMR = 16.1
	Glucose = 5.2 mmol/L	Mgluc = 9.3	
	Amylase = 128 mg%	Mam = 18,6	
Full blood test findings	Leukocytes = $22 \cdot 10^9$/l	Mleuk = 21.4	IIR = 14.8
	Stab neutroph. = 2 %	Mstab = 4.6	
	Segm. neutroph. – 62% Segm. neutroph. = 63.5% of the norm	Msegm = 20.1	
	Monocytes = 12%	Mmon = 13.0	
Cardio-vascular system	Syst. BP – 100 mm Hg Syst. BP = 48% of the norm	Msyst = 9.1	ICR = 9.5
	Diast. BP – 60 mm Hg Diast. BP = 45% of the norm	Mdiast = 7.8	
	HR – 100 beats per min HR = 54% of the norm	Mhh = 11.5	

Note: * – BMI – body mass index, z-score – body mass calculated in WHO ANTHRO Plus, stab neutroph. – stab neutrophils, segm. neutroph. – segmented neutrophils, syst. BP – systolic blood pressure, diast. BP – diastolic blood pressure, HR – heart rate;
** – Mbmi, Mgluc, Mam, Mleuk, Mstab, Msegm, Mmon, Msyst, Mdias, Mhr – modification coefficients of body mass index, glucose, amylase, leukocytes, stab neutrophils, segmented neutrophils, monocytes, systolic blood pressure, diastolic blood pressure, heart rate respectively;
*** – IMR – index of metabolic reactions, IIR – index of immunological reactions, ICR – index of cardio-vascular reactions.

corticosteroids (blood glucose); no parameters are mentioned that can act as early markers of adverse side effects of corticosteroids.

Sporadic metabolic side effects of corticosteroids in children with nephrotic syndrome are described in literature, for example, pancreatoxicity, obesity (Bekmurzayeva et al. 2012, Foster et al. 2006). However, no criteria for early detection of pancreatic damage during the corticosteroid therapy are given.

When taking glucocorticoids for a long period of time, some changes may occur in the full blood test parameters which are well known, i.e. a decrease in the number of lymphocytes, eosinophils, basophils with simultaneous development of neutrophil leukocytosis, persisting for 1-4 weeks (Landyshev 2014). The recommendations on monitoring children with nephrotic syndrome receiving glucocorticoid therapy include a demand to control full blood test parameters once in 10-14 days (Tsygin et al. 2006). However, no specific groups of parameters proving the influence of corticosteroids on the body are identified in these recommendations and check times are shown without considering early detection of glucocorticoid side effects (Aljebab et al. 2016, Pasini et al. 2015, Skrzypczyk et al. 2014).

Application of the developed indices will make it possible to diagnose early metabolic, cardio-vascular and immunologic changes in patients with nephrotic syndrome in the context of glucocorticoid therapy and perform their individual pharmacological correction in a timely manner.

Conflicts of interest

The authors have no conflict of interest to declare.

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