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TREATMENT OF IDIOPATHIC THROMBOCYTOPENIC PURPURA: PREVENTION OF HORMONAL COMPLICATIONS IN THE STOMACH AND DUODENUM

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ABSTRACT

Background. Idiopathic thrombocytopenic purpura (ITP) is a chronic disease which is accompanied with bleeding and decrease in platelet count due to its pathogenesis and treatment. The pathogenetic treatment of ITP is considered to be the use of glucocorticosteroid hormones. Clinical observations indicate that gastrointestinal tract complications such as acute gastritis, duodenitis, gastrointestinal ulcers or exacerbation of previously existing chronic pathologies may occur when patients with ITP take in glucocorticosteroid hormones per os in large doses for a long time. This study was performed to develop prevention methods of stomach and duodenum complications related to hormonal therapy in patients with ITP.

Materials and methods. Patients were classified according to the complications of

different disorders: gastroduodenitis - 22 (23.1%), gastric ulcers - 6 (6.3%), and duodenal ulcer (or exacerbation of the latter) - 5 (5.3%), exacerbation of colitis - 2 (2.1%), gastrointestinal discomfort - 10 (10.5%), stomach pain -5 (5, 3%). Totally, 50 (52.6%) out of 95 patients with ITP (both adults and children) were registered to have complications of gastrointestinal tract after enteral glucocorticosteroid administration.

Findings. It is recommended to transfer corticosteroid administration from per os to the form of inhalation or intravenous one. The relationship between number of platelets and the indication for the performance of an endoscopic examination of gastrointestinal tract along with gastric ulcer hemorrhage has been proven. Endoscopic examination of patients with TP is recommended to be carried out in the stage of clinical remission.

Key words: thrombocytopenia, glucocorticosteroids, acute ulcers, chronic ulcer, bleeding, hemorrhage.

INTRODUCTION

Idiopathic thrombocytopenic purpura (ITP) is a chronic autoimmune disease accompanied with bleeding. A decrease in the number of platelets due to their increased destruction is the main manifestation of the disease [1]. This disease is the most common autoimmune disorder involving blood cells [2]. Its incidence is estimated at 1.6 to 2.7 cases per 100 thousand individuals/year, and prevalence at 9.5 to 23.6 cases per 100 thousand individuals, with predominance of the female sex [3].

ITP is The decrease in the number and function of platelets which leads to bleeding is the most important complication of ITP. Bleeding is mostly seen in the skin and mucosa. Claire et al. found in their study that the most important complications of this disease include petechiae, anemia and extensive bleeding [4].

Gastrointestinal bleeding syndrome (GBS) exacerbates many of the alimentary tract diseases and it can also lead to death [5].

Erosive and ulcerative lesions of the stomach and duodenum take the first place among the causes of bleeding in the upper sections of GIT. Acute ulcers of GIT are observed at any age, both in newborns and in adults [5]. The frequency of acute ulcerative lesions in elderly people reaches 74.6% [6]. The detection of acute erosion and ulcers usually occurs when patients are examined for severe symptoms

of dyspepsia, but more often - when complications such as bleeding occur (60–70%), or acute ulcer perforation (0.5–3%). Acute erosion and gastrointestinal ulcers complicated by bleeding frequently occur in patients after glucocorticosteroid (GCS) therapy [7, 8]. The standard initial treatment for ITP is oral corticosteroids to increase platelet counts. This type of hemorrhage, which occurs after GCS treatment, is typical for predominant location of ulcers on the greater curvature of the stomach, multiple lesions, and a latent process.

Prednisolone (per os) is considered as a standard drug for pharmacodynamic therapy among GCS, especially in patients with immune thrombocytopenia [9]. Hormones cause general dysfunction of the gastrointestinal tract in 24.4% of cases, and the ulcerogenic effect, especially when administered orally, is manifested in 3.5-7.5%. Complications of GCS therapy in GIT are associated with the duration of this therapy, high doses and improper use of GCS hormones when administered per os [10, 11].

Idiopathic thrombocytopenic purpura (ITP) is an autoimmune disease in which the body produces antibodies against its own platelets and the spleen destroys these platelets. This causes the decrease in platelet count and leads to bleeding or hemorrhage syndrome. In the case of the significant decrease in platelet count, the risk of profuse bleeding increases with the development of severe posthemorrhagic anemia [12]. The disease proceeds in the acute form and does not recur later in 80% of children [13]. The chronic form of ITP is more likely to occur in adults. The disease often develops with no explicit connection with any previous disease [14].

The major clinical symptom is hemorrhage. The severity of the hemorrhagic syndrome is different - from single bruises and small petechiae to massive bleeding from internal organs and hemorrhage to vital organs and centers [15], “bruise flowering” is common for this disease. Generally, spontaneous hemorrhage syndrome develops when platelet count decreases below 50-30×109/L. In some cases, platelets may be completely absent in the blood [16].

Patients with ITP sometimes experience severe GIT hemorrhage which leads to anemia of patients and poses threat to their life. Hematuria along with hemoptysis are less commonly noted [17].

Some research analyses showed that gastrointestinal tract pathology before and after glucocorticosteroid (GCS) therapy is not well understood in patients with ITP. Available publications on this issue are episodic and do not give a complete picture of the gastrointestinal tract state in people with ITP. Complications of GCS therapy in GIT are associated with the duration of this therapy, high doses and improper use of GCS hormones when administered per os. The authors claim that the reason for the development of gastric ulcers during the treatment with GCS per os is hypersecretion of gastric juice [3, 6, 18].

The cause of the stomach ulcer progression is gastric hypersecretion. Acid-forming function of the stomach according to the data of intragastric pH-metry was significantly increased (pH=1.1±0.06) in all patients [19]. In some cases, gastrointestinal ulcers are complicated with perforation or hemorrhage after taking corticosteroid hormones [20]. According to published data [21], about 5% of patients with thrombocytopenic purpura (TP) have acute gastrointestinal bleeding. In intensive care units mortality rate of patients with gastrointestinal bleeding from acute ulcers reaches 80% [22], and the number of patients with thrombocytopenia grows every year. In addition, standard usual treatment begins with GCS hormone therapy (per os) [23]. Any mucous membrane damage leads to an increase or recurrence of the GIB during the acute period or relapse of thrombocytopenic purpura [24].

Taking into account distinct side effects of prolonged corticosteroid use per os, in order to reduce or prevent corticosteroid complications we are seeking other methods of corticosteroid administration. In this regard, the inhalation method of administering GCS hormones to patients with ITP is noteworthy, although we could not find any data regarding the study devoted to the GCS hormone inhalations in patients with ITP [25].

Given this method, the management of patients with thrombocytopenia complicated by GIB has its own characteristics. Therefore, the search for the development of methods for the prevention of relapse and complication, and methods of treating gastroduodenal hemorrhage during thrombocytopenia is today's topical problem in surgical hematology and general surgery [26].

MATERIALS AND METHODS

According to the data we obtained, the administration of GCS hormones per os often leads to gastrointestinal complications. Thus, our patients were classified according to the complications of different disorders: gastroduodenitis - 22 (23.1%), gastric ulcers - 6 (6.3%), and duodenal ulcer (or exacerbation of the latter) - 5 (5.3%), exacerbation of colitis - 2 (2.1%), gastrointestinal discomfort - 10 (10.5%), stomach pain -5 (5, 3%). Totally, 50 (52.6%) out of 95 patients with ITP (both adults and children) were registered to have complications of gastrointestinal tract after enteral glucocorticosteroid administration. [Table 1].

Table 1.

Complications of enteral administration of GCS hormones in patients with acute and chronic ITP (95 patients in total)

Diagnosis	**Number of patients**
Gastroduodenitis	22
Stomach ulcer	6
Duodenal ulcer	5
Colitis (exacerbation)	2
Gastrointestinal discomfort	10
Pain in the stomach	5
Total	**50 (52.5%)**

Bleeding from gastric and duodenal ulcers was noted in 6 (12%) patients. 10 (22.2%) patients had post hormonal erosive gastritis and gastric ulcer exacerbation, 3 (5.6%) patients were indicated to have chronic duodenal ulcers, 4 (13.8%) patients experienced steroid gastric ulcers, 3 (10, 3%) people had gastrointestinal discomfort, and 2 (5.6%) were noted to have colitis.

Gastric and duodenal ulcer hemorrhage was noted in history of 2 (5.6%) patients. At the time of admission, 6 patients with GIB had the following results of their examination: the platelet count was 1-23x10 9/l, pulse rate 90-124 beats per min. A/P - 110/65 to 90/60 mmHg. One of patients manifested posthemorrhagic anemia of a severe degree, 3 - moderate degree, and 2 patients experienced it in a mild degree. All patients received conservative treatment: restorative agents, hemostatic and vasoconstrictor drugs, corticosteroid hormones - prednisolone or dexamethasone in the form of inhalation, simultaneously treating erosion, gastric and duodenal ulcers. GCS were prescribed at the dose of 1-15 mg/kg per day. The duration of the disease ranged from 8 months to 26 years and during this period, patients received treatment from 1 to 10 or more times.

Parenteral administration posed difficulties in children because of the pain. Often each injection was accompanied by tantrums and crying.

Coagulogram indicates hypocoagulation in all cases. Myelogram reveals that: the bone marrow punctate in all patients is quite cellular, the type of hematopoiesis is normoblastic, the lymphocyte count is within normal parameters, sufficient number of megakaryocytes, most of which do not contain any plates. In patients with gastrointestinal bleeding, the platelet count was below $30x10^9$/L. Endoscopic examination of patients with gastrointestinal bleeding was carried out in one patient with prolonged gastrointestinal bleeding under intensive hemostatic therapy [Forrest 1B (F1 b)]. Injection types of endoscopic hemostasis are contraindicated due to the bleeding of the injection site). Endoscopic examination for the rest of patients was carried out after treatment with clinical remission [Forrest 2 A (FIIa) - Forrest 2 B (FIIb)].

Taking into account distinct side effects of prolonged corticosteroid use per os, in order to reduce or prevent corticosteroid complications we are seeking other methods of corticosteroid administration. In this regard, the inhalation method of administering GCS hormones to patients with ITP is noteworthy, although we could not find any data regarding the study devoted to the GCS hormone inhalations in patients with ITP.

Interpretation glucocorticosteroid administration in the form of inhalation.

We began the inhalation 1.5 hours after a meal. The patient rested before it. He did not take any other medicines. Objective examination: breathing was balanced. No pathology was detected in mucous membranes of the oral cavity and pharynx, (there are no signs of bleeding). Swallowing is without difficulties. A/P is normal.

Nebulizer [5, 9] (compressor inhaler "Boreal") was prepared for operation. 1.2 ml of S. prednisoloni and 1-2 ml of saline solution were poured into the flask for spraying. The nebulizer was closed, and a mouthpiece for oral inhalation was attached to it. Then the nebulizer was set to mode I (the plug was closed). Before starting the inhalation, the patient rinsed his mouth and his throat with boiled water (room temperature). The patient took the seating position, dressed lightly. It was explained to the patient that during the procedure one should not strongly tilt the body forward and be distracted by conversations, reading. He needed to breathe deeply and evenly. After a deep breath taken with his mouth, he should hold his breath for 2-3 seconds, and then breathe out through his nose. The duration of the procedure was 10 minutes. After the procedure, there were no complications and the patient was recommended to rest for 45-60 minutes, and then have a meal that was at room temperature (patients with thrombocytopenia are not allowed to eat hot food).

Patients with ITP received glucocorticosteroids in the form of dosed cold inhalation, in compliance with all the rules and techniques of inhalation. The duration of one inhalation was 5-10 minutes, the dose of the hormone was 1-2 ml (1.0-2.0 mg/kg weight), 2-3 times a day.

RESULTS AND DISCUSSION

No matter how carefully the drug, dosage regimen and type of therapy are chosen, it is usually not possible to completely prevent the development of certain side effects when using GCS. According to our data, enteral administration of corticosteroids hormones often caused complications in the gastrointestinal tract.

Bleeding due to thrombocytopenia often led to the development of posthemorrhagic anemia.

When administration of glucocorticosteroids was parenteral, there were bruises at the injection sites, 4 patients had a hematoma after intravenous administration. Three examined patients retained skin hemorrhagic manifestations in the form of ecchymoses. 2 patients with chronic gastritis treated in other departments of the Research Institute of Hematology and Blood Transfusion, experiences pain in the stomach area after taking GCS hormones per os. Their stool was black and the platelet count did not increase (<20.0 x 10^9/l). Hb - 92-95 g/l, red blood cells - 3.5-3.2 million, color indicator - 0.7-0.6, white blood cells - 5.0-4.7x10^9/l. Patient was transferred to inhalation of corticosteroids after their admission to the surgical department.

In 2 patients with thrombocytopenic purpura (33.3%), platelet count rose to 50 thousand and hemorrhagic syndrome in the form of GIB was stopped on day 2. Clinical remission was obtained on average on day 10.

In 4 (66.7%) patients, on average, platelet count reached 180 thousand on day 8. In all 4 patients, the phenomena of hemorrhagic syndrome in the form of GIB were stopped on day 2-3 of treatment. Also, clinical and hematological remission was obtained.

Hemodynamic parameters in all patients returned to normal. In two of them, hemoglobin level rose to normal, the rest were discharged with mild anemia.

The acute form of idiopathic thrombocytopenic purpura begins suddenly. A person develops abundant purpura on the skin and mucous membranes and has a fever. Light bouts of the disease disappear after a few days; severe ones may be lethal or take a chronic course. The characteristic signs of the disease are thrombocytopenia, purpura with hemorrhage in the mucous membranes of the nose, mouth, intestines, uterus, vagina, renal pelvis, and ureters. Hematemesis develops either as a result of blood ingestion which was released from the upper respiratory tract, or blood overflow in the stomach from its mucous membrane vessels. In cases of bleeding from the vessels of the small intestine, melena occurs.

The diagnosis of idiopathic thrombocytopenic purpura with an acute course complicated by hemorrhagic syndrome was verified based on clinical and hematological data.

All patients were prescribed hemostatic and vasoconstrictor drugs, potassium preparations, GCS, diet, as well as the corresponding regimen. GCS hormones (prednisone and dexamethasone in the form of solution) were taken by patients in the form of inhalation using a Boreal dual-mode compressor nebulizer at a dose of 0.5-2.0 mg/kg per day. As an example, we provide an extract from the medical history.

Example 1: Patient B. Sh. 18 years old. Case history No. 2838. Complaints at the time of admission: bruising of blue color in the extremities, pain in the epigastrium, black stool. Anamnesis: the patient had been ill for about 4 years, and had received hormonal treatment several times. The skin and mucous membranes are pale. Pulse - 86 beats. per min., blood pressure - 115/70 mmHg, The heart - without major changes. Lungs - vesicular breathing on both sides (no hemoptysis). The tongue is wet (oral cavity: no signs of bleeding). Abdomen is involved in the act of breathing, soft. There was pain in the epigastric region. The liver is not enlarged. The defecation is free, regular, and black. Examination: CBC, Hb - 93 g/l, red blood cells - 3.6 million, color indicator - 0.7, white blood cells - $5.0x10^9$/l, platelets - $18.0x10^9$/l, segmented neutrophils- 68%, eosinophils - 1%, lymphocytes - 25%, monocytes - 6%, ESR - 5 mm/h. Coagulogram: Kaolin Cephalin Clotting Time - 47″, prothrombin index - 90%, plasma tolerance to heparin - 13′40″, plasma fibrinogen - 2.22 g/l, fibrinolytic activity - 150′, blood clot retraction - 0.3.

The patient received the following treatment: hemostatic, bracing medicine and iron supplements, anti-ulcer therapy. His treatment was carried out for 5 days using 12 mg of dexamethasone inhalation. After 5 days: Hb - 121 g/l, platelets - 52.8 x 10^9/l, white blood cells - $6.0x10^9$/l, hemorrhagic syndrome stopped, there were rare skin ecchymoses. Patient discharged with clinical remission.

Explanation: inhalation administration of S. prednisolone and S. dexamethasone. We began the inhalation 1.5 hours after a meal. The patient rested

before it. He did not take any other medicines. Objective examination: breathing was balanced. No pathology was detected in mucous membranes of the oral cavity and pharynx, (there are no signs of bleeding). Swallowing is without difficulties. A/P is normal.

Inhalations were carried out with a "Boreal" inhaler in mode I with an aerosol particle dispersion of 0.8-2.0 μm, while the drug flow rate was 1 ml. in 3.5 minutes.

The patient underwent the following examinations: CBC and urinalysis, biochemical blood analysis, coagulogram, examination of the chest and gastrointestinal tract, ultrasound of the abdominal organs, endoscopic examination and bone marrow examination.

After such therapy, according to the hemogram,: Hb - 124 g/l, platelet count - $52.8x10^9$/l, white blood cell count - $6.0x10^9$/l. Against this background, hemorrhagic syndrome began to stop, only a few skin ecchymosis remained.

EFGDS (5^{th} day) - cicatricial and ulcerative deformation of the duodenum, chronic duodenal ulcer and fresh thrombus that is sometimes covered with spotty fibrin plaque along the lower wall (0.7x0.9 cm). In the pylorus, an acute ulcer at 13 hours (0.2x0.3 cm) is covered with fibrin. Mild catarrhal gastritis. Multiple erosions are observed in the gastric cardiac section.

Diagnosis: Idiopathic thrombocytopenic purpura, chronic course, acute stage.

Complication: Acute (steroid) erosion of the stomach, chronic duodenal ulcer with hemorrhage in the acute stage. Chronic moderate hemorrhagic anemia.

Figuring out the cause of gastrointestinal bleeding in case of chronic thrombocytopenic purpura is not difficult, since the patient is usually well aware of the diagnosis of his underlying disease. Profuse nosebleeds and purpura of the skin indicate that the disease is exacerbating. It is much more difficult to diagnose acute cases of the disease. Hemorrhages and ecchymoses on the skin and mucous membranes can be very mild or appear later than hemorrhage in the mucous membrane of the gastrointestinal tract. Diagnostic error can be avoided only if we

targetedly look for signs of purpura and evaluate blood coagulation rate and platelet count in each case of gastrointestinal bleeding.

In patients with CITP the disease duration ranged from 6 months to 17 years. Previously, they were hospitalized from 1 to 10 times, GCS received from 0.5 to 5 g or more. Petechiae, ecchymoses, nosebleeds, gingival bleeding, uterine bleeding, and gastrointestinal bleeding were observed in these patients. These manifestations of hemorrhage syndrome were often combined. Against the background of bleeding, these patients had mild or severe anemia. According to the coagulogram hypocoagulation was detected in all cases. Myelogram: the bone marrow punctate of patients is quite cellular, there are a lot of megakaryocytes, but mainly without signs of the plate existence. As an illustration, we provide an extract from the medical history.

Example II. Patient M.M., 17 years old. Case history No. 2890.

Complaints upon admission: weakness, fatigue, dizziness, headache, pain in the epigastric region, long and plentiful mensis, bruises and small rashes in the body, black defecation.

Anamnesis: sick for more than 1 year, received treatment several times with a temporary effect, received hormonal drugs per os, the above complaints appeared again in the last 2 weeks. The patient in the last 3 months had a steroid gastric ulcer. The condition of patients during admission is serious. The skin and mucous membranes were pale blue, small hemorrhagic rashes in the extremities, bruises of the palm size were more common on the lower extremities, at the injection site and in the front side of the abdomen. Subcutaneous fatty tissue was well-developed, the face was moon-shaped, lymph nodes were not palpable. Pulse - 100-110 beats per minute, rhythmic, blood pressure - 90/60 mmHg. The heart sound was muffled, systolic murmur at the apex was found. The lungs - vesicular breathing on both sides (no hemoptysis).

The tongue is moist (oral cavity - there are no signs of bleeding), the abdomen was enlarged due to the subcutaneous fat layer,takes part in the act of breathing, soft, experienced pain in the epigastrium, tense muscles, peritoneum irritation was

detected. The liver and spleen are not palpable. Pasternatsky's symptom is negative on both sides. The stool is free, regular, black. Urination is free and regular. The patient had mensis from the age of 14. In recent years it is irregular, bleeding lasted up to 2 weeks, and for 10 days they were abundant.

Examination: upon admission: Hb – 54 g/l, erythrocytes - 2.2 million, color indicator - 0.6, white blood cells - $5.0x10^9$ / l, platelets - rare.

Coagulogram: Kaolin Cephalin Clotting Time – 48″, PT - 67%, plasma tolerance to heparin – 19′, plasma fibrinogen - 1.99, fibrinolytic activity – 130′, retraction of a blood clot - 0.27. Biochemical analyzes: total protein - 58.5 g/l, total bilirubin - 23.7, direct - abs, indirect - 23.7 μmol/l, ALT - 1.1 μmol/l, AST - 0.5 μmol/l, HBsAg is negative.

Ultrasound - intravenous organs without abnormal features. ECG - sinus tachycardia, change in the left atrium, depolizing changes in the myocardium.

Based on these data, the diagnosis was established: idiopathic thrombocytopenic purpura, a chronic, often relapsing course.

Complications: steroid gastric ulcer, Cushingism, hyperpolymenorrhea. Posthemorrhagic anemia, severe form.

Accompanying disease: chronic hepatitis.

The patient received general strengthening and hemostatic therapy, riboxin, iron supplements and potassium preparations, red blood cells, and plasma.

A solution of dexamethasone of 6.0 mg per day was administered as an inhalation for 3 days and 7 days of 4.0 mg per day +4.0 mg intravenously.

General tests on the 3rd day of treatment: Hb - 114 g/l, red blood cells - 4.1 million, platelets - $34.1x10^9$/l, white blood cells - $4.1x10^9$/l, lymphocytes - 30%, ESR - 7 mm/hour.

EGDFS (3^{rd} day) - revealed a stomach ulcer.

The patient's condition improved, hemodynamics stabilized, stool color returned to normal. Petechiae on the body disappeared on the 5-6th day, the bruises decreased and some resolved, the color turned yellow-brown.

On the 14th day of treatment: Hb - 111 g/l, red blood cells - 4.0 million, platelets - 80.0x10^9/l, white blood cells - 4.0x10^9/l, segmented nuclei - 59%, lymphocytes - 39%, ESR - 8 mm/hour. Accordingly, positive shifts in the coagulogram. An operation – splenectomy - was performed after stabilization of the general condition of the patient. During the operation, blood loss amounted to more than 20.0 ml. After the operation, about 5 ml of blood was released through the drainage tube and the tube was removed on the 1st day. The postoperative course was smooth. Complete blood count after surgery: Hb -124 g/l, red blood cells - 4.0 million, platelets - 164.0x10^9/l, white blood cells - 5.4x10^9/l, segmented nuclei – 76, lymphocytes - 14.0%, ESR - 3 mm/hour. Coagulogram: Kaolin Cephalin Clotting Time - 37″, PT - 95%, plasma tolerance to heparin - 10′, retraction of a blood clot - 0.4. Discharged on the 9th day after surgery in satisfactory condition, with clinical and hematological remission.

Clinical observations indicate that in patients with ITP when taking GCS hormones per os in large doses, as well as for a long time, complications from the gastrointestinal tract can occur, intramuscular administration is complicated by hematoma, intravenous administration in most cases is difficult due to fragility of blood vessels and Cushingism.

However, recently there has been evidence on shorter courses of high-dose steroids such as dexamethasone. The rationale for the use of dexamethasone is based on the ability to provide an equivalent amount of corticosteroid therapy, but with a shorter exposure period. The standard dose is 40 mg per day for 4 days, courses are repeated monthly depending on the number of platelets [23].

An increase in the secretory gastric activity, microcirculatory disorders, as well as the anti-inflammatory effect of hormones are important in the damage of the gastrointestinal tract from GCS hormones. The normal hormonal activity of the adrenal cortex is necessary for the normal secretory activity of the gastrointestinal tract. GCS not only cause development, but also inhibits the healing process of existing ulcers. Experimental reproduction of acute insufficiency of the adrenal cortex causes suppression of secretion and violation of the mucous membrane with

the development of ulcers. The resistance of the mucous membrane to the action of ulcerogenic gastric factors, undoubtedly, decreases under conditions of hormonal insufficiency.

Based on these pathogenetic mechanisms of gastrointestinal tract complications formation from GCS hormones in patients with ITP, it can be assumed that taking hormones per os in patients with acute ITP increases the secretory gastric activity, improves their appetite and subsequently increases body weight. Microcirculatory disorders also occur as a result.

In the case of thrombocytopenia vascular endothelium, deprived of the angiotrophic function of platelets, becomes porous, brittle,with increased permeability, especially in patients with severe hemorrhage syndrome. Large doses of GCS hormones with their multiple prescriptions per os slow down the healing of the affected areas of the gastrointestinal tract and lead to an exacerbation of the pathological processes in it. Long-term hormone replacement therapy for CITP causes insufficiency of the adrenal cortex, which in turn suppresses the secretion of the gastrointestinal tract, contributes to the disruption of the mucous membrane contiguity and the development of gastritis, duodenitis or ulcers in the gastrointestinal tract [12].

Ultimately, all this reduces the effectiveness of the hormonal treatment of ITP, because when the gastrointestinal tract is damaged by GCS hormones, the sufficient number of them does not enter the bloodstream [13].

In particular, the administration of GCS hormones is contraindicated with an existing ulcer in the gastrointestinal tract because of the risk of internal bleeding. These shortcomings of GCS hormones, for example, in the treatment of ITP, lead to the appointment of additional drugs against enteric complications [9]. This increases the bed days, and often contributes to the transition of the acute form to the chronic, and the chronic form often gives relapses [21].

However, gastric discomfort, nausea, other dyspeptic complaints while taking GCS aren’t often associated with the damage to the gastric mucosa. Naturally, various gastrointestinal tract damages, which occur due to the administration of

GCS hormones, negatively affect the results of ITP treatment [7, 11]. Patients with ITP are usually transferred to parenteral administration of drugs when oral administration of GCS hormones causes complications of the gastrointestinal tract. Doses of GCS hormones increase 3-4 times when they are administered parenterally and patients receive them in several doses. In this case, GCS act shortly and are quickly excreted through the kidneys [6, 18].

Intravenous administration of GCS hormones to children (often several times a day) is accompanied by screaming, crying and psychosis, in obese patients - by an increase in blood pressure, in patients with Cushing's syndrome it is difficult to get into a vein [23].

Based on the foregoing, it is now necessary to improve the treatment of ITP in order to increase their effectiveness. To prevent the gastrointestinal tract complications, mental injuries in children observed during intravenous administration of GCS, and to optimize the effectiveness of GCS therapy in patients with ITP, we tested a new approach based on inhaled administration of GCS.

Indications for inhalation therapy of corticosteroids were:

- A history of gastric ulcer, duodenal ulcer, or ulcerative colitis;
- the emergence of steroid gastritis or gastric ulcer;
- the presence of the gastrointestinal tract hemorrhage;
- hypertonic disease;
- the appearance of frequent gastrointestinal discomfort associated with taking GCS per os;
- neurosis, hysterical state of children associated with the use of GCS intravenously and per os.

Extensive hemorrhage or an infected wound in the area of large saphenous veins. Contraindications to inhalation therapy of corticosteroids in patients with ITP disease were defined as following:

- severe general state of patients against the background of the primary disease;

- cardiovascular failure;
- respiratory failure;
- hepato-renal failure;
- intolerance to inhaled corticosteroids;
- children under 3 years old - relatively.

Furthermore, only 10% of the total amount of the drug substance was sprayed out through the inhalation system. Approximately 50% of GCS hormones in the form of a cloud enter the deep sections of the respiratory tract and bloodstream, and up to 40% of the dose is deposited in the oropharyngeal region and is swallowed, while about 10-20% of the drug is eliminated during expiration. As a result, approximately 0.7-0.8 ml (70-80%) out of 1 ml of the drug enters the patient's body. Whereas, corticosteroid hormones, when taken per os, are absorbed from the gastrointestinal tract into the hepatic bloodstream, where most of them (up to 80%) are inactivated. The drug enters the systemic circulation mainly in the form of inactive metabolites. Therefore, the systemic bioavailability of GCS, when taken orally, is considered very low.

Peculiarities of the pharmacokinetics and pharmacodynamics of glucocorticosteroid drugs administered by the aerosol route suggest that this method can come near to the intravenous method in terms of administration speed and pharmacological activity, significantly exceeding the latter in terms of the duration of the clinical effect [1, 4].

The treatment effectiveness level for patients with ITP was evaluated using the following parameters:

1. Clinical and hematological remission - an increase in platelet count >150x10^9/l and the disappearance of all hemorrhage syndromes.

2. Clinical remission: A - increase in platelet count up to 50x10^9/l or more; B - an increase in the number of platelets up to 30-50x10^9/l, with a slight hemorrhage syndrome.

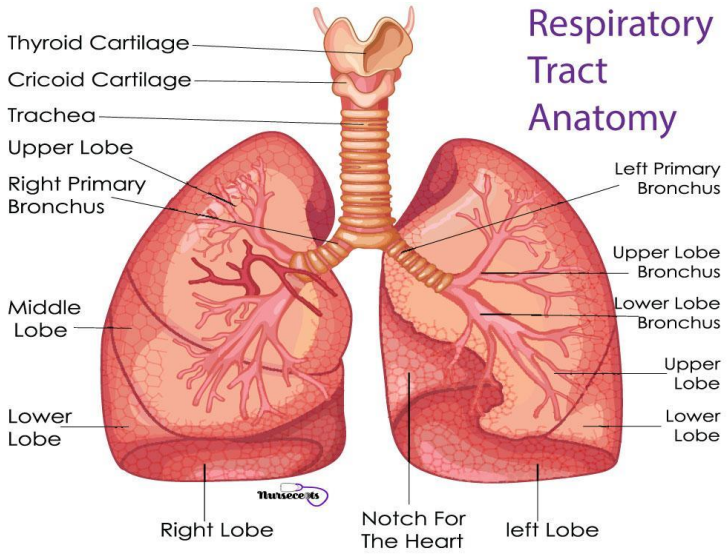
3. Lack of response - an increase in platelet count by less than 20x10^9/l, while maintaining hemorrhage syndrome.

4. Complete lack of response – platelet count <10x10^9/l with severe hemorrhage syndrome.

Inhalation therapy is a method of treatment by inhalation of drugs using special devices. *In medicine, aerosols are subdivided according to particle size into high-, medium- and low-disperse. The smaller the aerosol particles, the longer they remain in the stream of inhaled air and the deeper they penetrate in the respiratory tract [10, 11].*

Respiratory bronchioles, alveolar passages and alveolar sacs form a single alveolar tree or respiratory parenchyma of the lung. They form its functional anatomical unit, called the acinus (bunch). The number of acini in both lungs reaches 800,000, and the alveoli - 300-500 million, the walls of which are penetrated by blood vessels: arterioles and capillaries. It is estimated that if you expand the walls of the alveoli, they will cover a surface of 90 m^2. The area of the respiratory surface of the lungs ranges between 30 m^2 when exhaling to 100 m^2 during inhalation. Acini aggravate and form lobules, lobules form segments, segments - lobes, and lobes — the whole lung (Fig. 1)

Fig. 1. Respiratory (respiratory) system



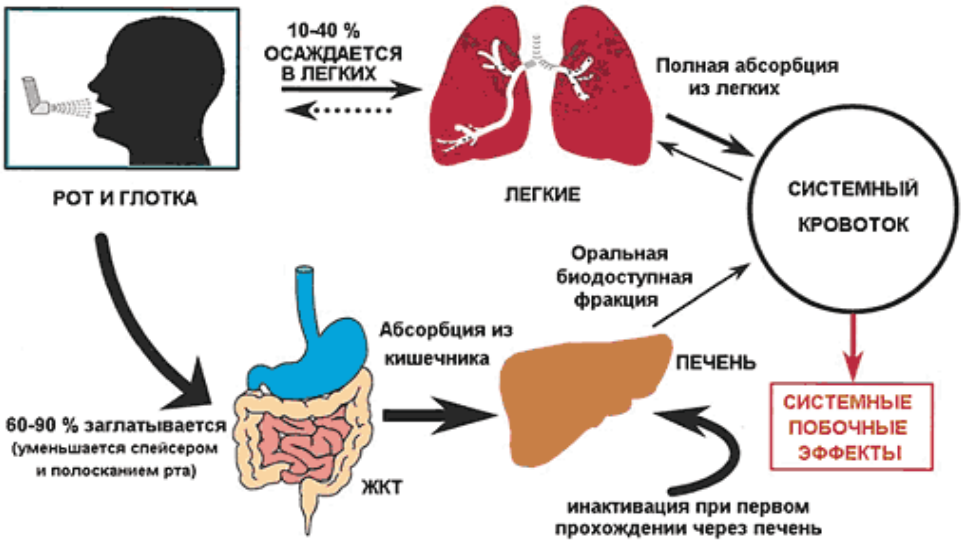
In this regard, the advantages of inhalation therapy over other methods such as intramuscular or intravenous administration are in faster and more absolute

absorption of drugs compared to the way through the gastric mucosa, This method increases the active surface of the drug, depositing it in the submucosal layer (rich in blood and lymph vessels), and contributes to the creation of high concentrations of drugs directly in the lesion area. While other methods of drug administering, cause them to be partially destroyed by liver enzymes, without crossing the protective barrier of the liver.

Therefore, the delivery of drugs to the lungs by inhalation is more logical and rational when drugs in the form of aerosols directly enter the target organ [9, 14]. The safety of IGCS is significantly higher than oral GCS due to their local action, as well as rapid presystem inactivation. However, the initial point of view that a direct delivery method can protect against the development of undesirable effects is no longer so unambiguous. IHCS enter the systemic circulation by being absorbed from the digestive tract and lungs. Approximately only 10–40% (depending on the delivery method) of the entire dose is precipitated in the lungs, where they are completely absorbed (pulmonary bioavailability). A more efficient delivery of inhaled corticosteroids to the lungs is thus accompanied by an increase in systemic absorption, but it can be compensated by a reduction in the dose necessary for optimal control of the inflammatory process. The rest of the inhaled dose (60–90%) is precipitated in the mouth, is swallowed and absorbed from the digestive tract. Fortunately, a large proportion of it undergoes inactivation the first time it passes through the liver, and only a small portion, the oral bioavailable fraction, enters the systemic circulation. Using spacers, rinsing the mouth after inhalation reduces the risk of undesirable effects [1, 8] (Fig. 2).

Fig. 2. The mechanism of systemic bioavailability of IGCS.

According to D. Allen.



According to Avdeev SN et al., pulmonary deposition of drugs using various delivery systems is 4-60% of the measured dose. By using a radioactive tracer, it was found that measured aerosol inhalation reaches 21-45% during pulmonary drug deposition in inhalation through a spicer system aerosol.

The use of prednisolone and dexamethasone solutions in inhalations in the respiratory system pathology showed that the acid-forming function of the stomach remains normal or decreases slightly. The use of these hormones through a nebulizer accelerates recovery 1.5-2 times, reduces the use of systemic hormones and improves the quality of treatment [2, 4, 9].

Inhalation (nebulizer from Lat. Nebula - fog, cloud) therapy has the following advantages:

- the possibility of inhalation of high doses of drugs;

- deposition of a small fraction of the preparations in the oral cavity and pharynx;

- simplicity of inhalation technique;

- lack of propellants that irritate the respiratory tract;

- the possibility of the oxygen and mechanical ventilation inclusion into the supply circuit

- “comfort” for patients: a nebulizer allows you to quickly achieve a clinical effect, while avoiding such unpleasant procedures as intravenous administration and taking per os a large number of tablets.

GCS hormone inhalation was performed per os or nasally. Inhalation was carried out through the mouth when the patient experienced nosebleeds due to tampons in the nasal passage, through the nose - during gingival bleeding, in most cases through the nose – during absence of bleeding from the above points.

Based on these pathogenetic mechanisms of gastrointestinal tract complications formation from GCS hormones in patients with ITP, it can be assumed that taking hormones per os in patients with acute ITP increases the gastric secretory activity, increases their appetite and subsequently increases body weight. As a result, microcirculatory disorders also occur.

During thrombocytopenia vascular endothelium, deprived of the angiotrophic function of platelets, becomes porous, brittle, increases its permeability, especially in patients with severe hemorrhagic syndrome. Large doses of GCS hormones per os slow down the healing of the affected areas of the gastrointestinal tract and lead to an exacerbation of the pathological processes in it. Long-term hormone therapy for CITP causes insufficiency of the adrenal cortex, which in turn inhibits the secretion of the gastrointestinal tract, contributes to the violation of the integrity of the mucous membrane and the development of gastritis, duodenitis or ulcers in the gastrointestinal tract, sometimes accompanied with bleeding [3, 12].

CONCLUSION

No matter how carefully the choice of the drug, the dosage regimen and the type of therapy are carried out, usually it is not possible to completely prevent the development of certain side effects when glucocorticosteroid hormones are used.

Clinical observations indicate that gastrointestinal complications may occur in patients with TP when taking GCS hormones per os in large doses, as well as for a long time. GCS not only cause the development of ulcers, but also inhibits the

healing of existing ulcers. Experimental reproduction of acute insufficiency of the adrenal cortex causes suppression of secretion, a violation of the mucous membrane with the development of ulcers. The resistance of the mucous membrane to the action of ulcerogenic factors of the stomach, undoubtedly, decreases under conditions of hormonal insufficiency

Large doses of corticosteroid hormones with their multiple prescriptions per os slow down the healing of affected areas of the gastrointestinal tract and lead to an exacerbation of the pathological processes that are present in it. Long-term hormone therapy leads to insufficiency of the adrenal cortex, this, in turn, inhibits the secretion of the gastrointestinal tract, leads to a violation of the integrity of the mucous membrane and the development of gastritis, duodenitis or ulcers in the gastrointestinal tract. Vascular endothelium with thrombocytopenia, deprived of the angiotrophic function of platelets, becomes porous, brittle, increases its permeability, especially in patients with severe hemorrhagic syndrome and hormonal lesions of the gastrointestinal tract, often complicated by bleeding.

Given this, hormonal drugs are transferred from per os to inhaled. An endoscopic examination is performed with ongoing gastrointestinal bleeding under enhanced hemostatic therapy. Any additional trauma during endoscopic examination can become a source of bleeding, including local endoscopic hemostasis. Further endoscopic studies and treatment should be carried out after normalizing the number of platelets and their function in the blood.

There is a definite correlation between platelet count and clinical manifestations. With a platelet count of above 30-50x109/l, the course of the disease is often asymptomatic. When the platelet count is below $30x10^9$/l, hemorrhage complications appear. You need to know that determination of the hemorrhage cause is only possible using laboratory methods.

Inhaled administration of GCS hormones in dosed cold form on the “Boreal” nebulizer device to patients with acute and chronic forms of ITP is an alternative to the existing traditional method of conservative treatment. Thanks to the inhalation

method, it is possible to prevent a number of corticosteroids therapy complications and the transmission of parenteral blood-borne infection.

Inhalation administration of corticosteroid hormones is indicated especially for children with ITP and people with gastrointestinal tract diseases. Contraindications are a severe general state against the background of the primary disease and intolerance to inhaled corticosteroids.

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