

Algorithm of Management of a Patient with Acute Cholestatic Hepatitis

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Abstract: Laparoscopic cholecystectomy (LC) is one of the commonest elective laparoscopic procedures performed. In the United Kingdom, these procedures are performed widely through the National Health Service. Whilst a few years ago, patients remained in the hospital for 1 or 2 days after uncomplicated LC, increasingly this procedure is being performed on an outpatient basis. Improved primary care support and increasing financial pressures have also diminished the postoperative follow-up of these patients by the operating surgeon. In essence, the operating surgeon is no longer involved in the postdischarge care and follow-up of patients undergoing LC. Though major complications after LC are well recognized, data about the process of patients' short-term recovery after hospital discharge, perceptions of well being, and the burden of postoperative care required in the community are not documented. Knowledge of this unobserved recovery phase is not only vital to organizing a community care package and improving service delivery and patient satisfaction, but also is very relevant feedback, which the operating surgeon misses in today's world. We hence performed this study with an aim to follow up patients closely after uncomplicated LC to document the postoperative symptoms, assess their perceptions regarding return to preoperative routine and estimate the postoperative care they required from the community health services.

Keywords: cholestasis, plant-based preparations, herbs, biologically active additives, hepatotoxic, side effects.

The study cohort comprised 102 patients who all completed the study. Postoperatively, only 2.9% of the patients had postoperative nausea/vomiting lasting ≥ 2 days. Pain was symptomatic in 11.7% of patients. Port-site wounds were a source of significant symptoms in 70.5% of the patients. Postoperative review by a community nurse and primary-care doctor were necessary in 77.4% and 32% patients, respectively, with a combined average of 3.1 reviews per patient. Less than 4% of patients believed that they would benefit from a surgeon's review 6 weeks after LC. Median time taken to return to routine preoperative activity after surgery was 22 days (IQR, 17 to 34), which was affected by the degree of activity undertaken, wound-related symptoms persisting for ≥ 3 weeks, planned follow-up clinic appointment, and discharge as an outpatient.

The first comprehensive essay on medicinal plants that has come down to us, in which the scientific justification is given—their application belongs to the greatest thinker, a doctor of ancient Greece, one of the founders of modern scientific medicine, Hippocrates (460-377 BC). In it, he described 236 medicinal plants that were then used in medicine. In ancient times, herbal treatment was the patient's only chance of healing, and at present it is difficult to predict the harm/benefit ratio, since there is no data on the standards for collecting plant parts, their storage and use.

Reliable clinical studies on the safety and tolerability of phytopreparations have not been

conducted, therefore, there are no such concepts as "recommended dose", "toxic dose", "excess dose". Clinical trials aimed at studying the mechanism of action of phytopreparations and evaluating their effectiveness are difficult to conduct mainly due to the variety of composition (formulas) and dosages. No wonder the famous physician and philosopher of the Renaissance Paracelsus said: "Everything is poison, and everything is medicine. The dose alone does the substance is either poison or medicine." Nevertheless, most patients consider natural medicinal plants to be completely harmless, and phytopreparations to be medicinal products (drugs) that do not have adverse reactions. Unfortunately, this does not always correspond to reality.

1. The efficacy and safety of medicinal plants are actively investigated by pharmacologists, and the toxicity aspect of widely used plants is well known [7]. From a pathogenetic point of view, all undesirable effects of drugs (including phytopreparations, various herbs, herbal preparations and tinctures) can be divided into the following variants [2-4, 12, 20]: Hypersensitivity:

2. allergy,

➤ pseudoallergia,

➤ idiosyncrasy;

Toxicity. Toxic reactions are realized through a direct damaging effect on the liver cells. At the same time, the dependence on the dose of the substance received into the body, as well as on the time of its exposure, is clearly traced. The appearance of an allergic reaction does not depend on the dose of the allergen. Unlike allergies, a pseudo-allergic reaction can develop already at the first administration of the substance. At the same time, specific sensitizing antibodies are not detected and dose dependence is detected, although not as pronounced as in the case of toxic action. Idiosyncrasy, as a rule, is caused by congenital defects of the biochemical or enzyme systems of the body, leading to a sharp disruption of the metabolism of certain substances, including herbal preparations. A pathological reaction occurs at the first exposure, while dose dependence is also noted. [2, 12]. To date, more than 50 hereditary metabolic diseases are known, which are characterized by extremely high sensitivity to certain drugs [2]. The generally accepted view of the pathogenesis of medicinal-induced liver damage suggests that some plant components turn into hepatotoxins in the process of metabolism, which is mainly carried out by the liver P-450 system - more than 50 isoenzymes encoded by individual genes [2, 4]; an individual reaction develops to them intolerance is an idiosyncrasy. It is also possible to disrupt the integrity of mitochondrial membranes, which triggers apoptosis reactions [12,]. Drug-induced hepatopathies occur unpredictably due to individual characteristics of pharmacokinetics and are not dose-dependent [2, 4, 12,]. Hepatotoxic reactions to homeopathic drugs are explained in a similar way [5, 8] of the Automated Information System of Roszdravnadzor received 6057 reports of adverse adverse reactions (NPR) and drug inefficiency. Compared to 2008, the number of reports on NPR in the territory of the Russian Federation has increased almost 5 times [1]. Data on the frequency of adverse reactions associated with the use of herbal remedies, herbs and biologically active additives (dietary supplements) are not provided. Often, the patient and the doctor do not associate the side effects that have arisen with the herbal preparations taken, and the "medical history" remains in the shadows.

For example, in the Russian Federation, the plant raw material "Celandine grass" (*Chelidonii herba*) was registered - a plant that the patient we observed used as a prevention of oncological diseases. The pharmacological activity of celandine bolshogo (CB) has been studied quite fully [5]. It is mainly caused by alkaloids – helidonin (the main one), homochelidonin, protopin, sanguiritrin (the sum of the alkaloids sanguinarine and helerethrin). In the pharmacy chain, celandine herb is available in boxes, packs and filter bags, several homeopathic preparations of varying degrees of dilution for the treatment of mainly pathology of the hepatobiliary system, external

parapharmaceuticals [7].

Increased attention to CB arose after J. Benninger et al. described a series of 10 cases of chelidonium acute hepatitis, which they observed in the period from 2017 to 2019 [13]. The severity of hepatitis was moderate, the results of a liver biopsy performed in some patients resembled those of a medial lesion of the organ parenchyma by type of cholestasis. Patients went to the doctor due to a change in skin color and the appearance of itching; there was a moderate course of the disease with a moderate increase in the activity of liver enzymes in the blood; complete recovery after discontinuation of the drug was observed after 2-6 months. It is significant that repeated use of CB by one of the patients led to a relapse of hepatitis [18]. This report is the first detailed description of the hepatotoxicity of celandine herb, which, paradoxically, was used as a hepatoprotective agent.

This was followed by other descriptions of cases of hepatitis caused by the use of CB. All of them were diagnosed due to the fact that patients developed cholestatic syndrome (jaundice, itching of the skin) [7]. P. Bergner suggested the following mechanism of the established hepatotoxic effect [14]. CB has a double effect: it is choleric and cholekinetic. But its cholekinetic effect is much reduced during storage and completely disappears after 6 months, while the effect on secretion remains unchanged. Since most of the preparations are made from raw materials that have been stored for a long time, the induction of secretion significantly prevails over the antispasmodic effect. Against the background of the presumed idiosyncrasy of patients to the active substances of CB, cholestatic hepatitis develops. In the clinical observation described by P. Bergner, hepatitis recurred after the patient resumed taking CB [7, 13].

The causes of adverse reactions, as well as their number, are largely due not only to the direct effect of the drug taken, but also to the age and gender of the patient, the severity of his condition and concomitant diseases. Do not forget about the genetic component of hypersensitivity.

It is impossible to ignore the role of various bio-additives to food, which are not formally medicinal products, but are considered as means for the treatment of a wide range of diseases, including liver. The danger of dietary supplements in relation to damage to the liver and other organs is due to [3, 6]:

- a multicomponent composition that does not allow to isolate a specific substance responsible for the development of a pathological reaction;
- lack of strict control over non-lethal effects and their mandatory registration. The hepatotoxicity of phytopreparations and herbal preparations can be caused by the potentiation of the adverse effect on the liver of several herbs with their unsuccessful combination (simultaneous administration), as well as be the result of a number of additional factors. For example, the effects of the same plant ingredient vary depending on the geoclimatic conditions of the growing region of the plant. If there are too many ingredients in the formulation of phytopreparations, the unpredictability of their total effect arises, which negatively affects, first of all, in children's practice and in persons with a burdened allergic history.

Currently, there is no reliable data on the adverse role of a number of phytopreparations, and the mechanism of their action has yet to be studied. All adverse effects of herbal preparations can be classified as follows: plants with proven hepatotoxicity; plants whose hepatotoxicity is disputed; plants suspected of hepatotoxicity; plants containing hepatocarcinogens (Gorchakov V.N., 2003). Do not forget that the so-called "impurities" included in the ingredients can be potentially toxic, i.e. chemical compounds that enter the plant during fertilization, insecticide treatment, environmental pollution. It should also be mentioned about such unpleasant effects of phytopreparations on the body as the development of mental and physical dependence. Despite the fact that, based on the current legislation, phytopreparations and dietary supplements cannot contain ingredients with such

effects, unfortunately, the current control system does not always guarantee protection against such.

There is still no unified system of standardization of phytopreparations, there is no control and clinical studies on their use, the effects on the body have not been fully studied. The patient and the doctor need to remember that any herbal preparations, infusions, dietary supplements and phytopreparations, which are now so widely used by the population, can have a toxic effect, including hepatotoxicity. Since medicines, as well as active substances in herbs, phytopreparations and dietary supplements belong to xenobiotics, the neutralization of which occurs in the liver, their uncontrolled intake can lead to liver damage.

This clinical observation demonstrates, on the one hand, the consequences of uncontrolled use of drugs, and on the other, reveals the tactics of managing a patient with acute cholestatic syndrome.

Conclusion. In the submitted case a main role in recognition of an etiology of liver disease have played by careful taking of past history and analysis of all possible causes of disease, that can be the key point in diagnostic search and choice of patient management tactics.

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