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DAMAGE TO THE DIGESTIVE SYSTEM WHEN USING NON-STEROIDAL ANTI-INFLAMMATORY DRUGS

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Summary. *Discussion of the side effects of the group of drugs most in demand in modern clinical practice - non-steroidal anti-inflammatory drugs (NSAIDs) - is traditionally limited to a discussion about the potential (according to therapists) or real (according to surgeons) danger of the toxic effect of these drugs on the gastrointestinal mucosa. However, as the digestive tract is not limited by the mucous membrane of the stomach and intestines, so the spectrum of side effects of traditional NSAIDs on the part of the digestive system is not limited to their gastrotoxicity. An equally significant problem associated with the widespread use of NSAIDs is their hepatotoxic potential. The hepatotoxicity of NSAIDs, not appearing to most modern researchers as an exception to the rule or an artifact, today is the subject of close study at the level of national health departments [6,13,22,27]. At first glance, the targets of the toxic effects of NSAIDs are different - the mucous membrane of the digestive tube and the hepatic parenchyma.*

However, it would be too simplistic to talk about the multidirectional side effects of this group of drugs. It seems that the gastro- and hepatotoxicity of NSAIDs are links in the same pathogenetic chain, which can result in massive hemorrhages from the upper digestive tract. This complication is already in the competence of surgeons, which determines the possibility of presenting the concept of the pathogenetic relationship of gastro- and hepatotoxicity of NSAIDs to a representative of this specialty.

The key points of this pathogenetic model are: direct toxic effect of NSAIDs on intact or pathologically altered hepatic parenchyma with the emergence of acute or worsening chronic hepatic failure, portal gastropathy in patients with liver cirrhosis and portal hypertension syndrome, NSAIDs-induced damage to the mucous membrane of the gastroduodenal zone.

Direct toxic effect of NSAIDs on the liver. Medicinal damage to the liver, including NSAIDs, is one of the serious problems of modern hepatology. This is due not so much to the frequency of occurrence of adverse reactions, as to the high probability of adverse outcomes in the event of their occurrence: up to 25% of all cases of fulminant hepatic failure are associated with drug damage to the liver. NSAIDs, being from a chemical point of view, an extremely heterogeneous group of drugs, have a similar therapeutic effect and cause the same type of side effects. N. O'Connor et al. (2003), based on the study of the epidemiological aspects of hepatotoxicity of non-steroidal drugs, concluded that almost all modern NSAIDs have qualitative hepatotoxicity, quantitatively expressed to a greater or lesser extent. Despite the fact that the relative risk of clinically significant liver damage due to the use of NSAIDs is relatively low (8–27 cases per 100,000 patients per year), the consequences of the emerging NSAID-induced liver damage often become the most serious: fulminant liver failure and hepatorenal syndrome [35]. These

undesirable side effects of NSAID therapy, which ultimately resulted in the death of patients or the need for emergency liver transplants, led to the prohibition of the use in clinical practice of benoxaprofen, droxicam, bromfenac, pirprofen, fenclofenac and in a number of states nimesulide [10,11, 15,17,21-23,31,33,36,38-40,42,45].

It is believed that damage to the hepatic parenchyma due to taking NSAIDs can occur at different times: immediately after the start of therapy, during a two to three week course of treatment, weeks or even months after its completion. P. Aithal et al. (1999) believe that most often clinical and laboratory manifestations of NSAID-induced liver damage are in the range of 6–12 weeks from the start of therapy. I. Lacroix et al. (2004), analyzing the features of the clinical manifestation of acute liver injuries associated with the intake of NSAIDs, notes that in 5–27% of patients, such injuries are asymptomatic and can be detected only by an increase in plasma transaminase activity [9,21]. Most researchers emphasize that the risk of drug damage to the liver increases in the presence of chronic diffuse liver disease of any etiology. In this case, the violation of drug metabolism is directly proportional to the severity of chronic hepatic cell failure [4,22,35,41,48].

As H. Tan et al. (2007), the clinical and morphological forms of the toxic effects of NSAIDs on the liver are very variable: acute hepatitis, cholestasis, cholestatic hepatitis, which tends to become chronic, granulomatous hepatitis, chronic cholestasis with ductopenia, yellow atrophy of the liver, manifested by fulminant liver failure. The authors believe that the most characteristic feature of the morphological picture in NSAID-induced liver damage is the combination of extensive hepatocellular necrosis with periportal mononuclear infiltration and a cholestatic component (Fig. 1) [48].

Despite a considerable number of studies devoted to the problem of NSAID-induced hepatotoxicity, the actual mechanism of damage to the hepatic parenchyma at the cellular and subcellular levels remains a subject of discussion today [5].

N. O'Connor et al. (2003) cites the two most frequently mentioned causes of NSAID hepatotoxicity in the literature: 1) hypersensitivity reactions, 2) metabolic damage (aberration). About the possibility of NSAID-induced liver damage, which is a consequence of hypersensitivity reactions (allergic reactions), according to R. Greaves et al. (2001), evidence of the development of "cross" toxicity with separated in time courses of therapy with chemically similar drugs (diclofenac - tiaprofenic acid), as well as the fact of the clinical manifestation of hepatotoxicity in the drug with a repeated course of therapy [20,34]. R. Bort et al. (1999), based on a generalization of experimental data, presented the sequence of events in hepatocyte injury by NSAIDs as follows. The main target of NSAIDs at the subcellular level is mitochondria. In the process of metabolism of NSAIDs by cytochrome P450, NSAID derivatives are formed (for example, 5-hydroxydiclofenac and n, 5-dihydroxidiclofenac), which are able to influence the processes of electron transfer in the respiratory chain on mitochondrial cristae, leading to a violation of oxidative phosphorylation, ATP synthesis and energetic in a cage. It is possible that native NSAIDs also have a toxic effect on mitochondria. Disruption of the processes of oxidative phosphorylation in mitochondria and microsomal oxidation of some NSAIDs (for example, naproxen) lead to activation of free radical oxidation, peroxidation of membrane lipids, NADPH and thiol groups of proteins, which ultimately results in membrane disorganization, death of hepatocytes and syntopic cellular structures (bile duct cells) [14,26-30]. It is possible that in the process of disorganization, the cytolemma acquires antigenic properties, which leads to the induction of an autoimmune response and morphologically manifests itself as periportal edema and mononuclear infiltration.

Speaking about the therapy of patients with NSAID-induced liver damage, it should be recognized that there are currently no means and methods that fundamentally affect the outcome of treatment. Treatment is carried out according to the standard scheme and consists in the abolition of NSAIDs, the creation of a protective regimen for the patient in compliance with the diet and limitation of physical activity, the appointment of hepatoprotectors, vitamins, antioxidants and in monitoring the dynamics of liver function tests. With the development of fulminant hepatic failure and hepatorenal syndrome, mortality reaches 80%, despite intensive post-syndrome therapy, including extracorporeal detoxification. Glucocorticoids may be useful in the overt allergic nature of hepatotoxicity, but their effectiveness has not been proven in controlled trials. Theoretically, they can be used in patients with a positive antinuclear factor or in viral etiology of previous NSAIDs — damage to chronic diffuse liver disease [1,2,6,38,47]. In severe cholestasis associated with the use of NSAIDs, the appointment of ursodeoxycholic acid in combination with duphalac may be effective [34,47]. In any case, clinically significant NSAID-induced liver damage requires control and correction of the hemocoagulation system. Almost all foreign authors consider the occurrence of acute liver failure as a result of NSAID therapy as a direct indication for urgent liver transplantation as the only effective therapeutic measure that can save the patient's life.

The possibility of monitoring specific markers of liver damage during NSAID therapy also seems difficult to implement: it is unclear in which patients, exactly, how often and for what period should be monitored. In fairness, it should be noted that the risk groups, where the manifestation of the hepatotoxic potential of NSAIDs is most likely, are presumably identified. According to L. Garcia – Rodriguez et al. (1994) C. Sgro et al. (2002), I. Lacroix et al. (2004), risk factors for the development of NSAID-induced liver damage should be attributed [18,21,46]: female patient, age over 56 years, the presence of chronic autoimmune disease, the presence of chronic diffuse liver disease, decreased renal function, hypoalbuminemia , therapy with high doses of NSAIDs, the presence of a chronic disease requiring NSAIDs, polypharmacy. On the other hand, perhaps, from a clinical, and even from an economic point of view, it is more expedient not to passively control possible manifestations of hepatotoxicity (which can very quickly become an uncontrolled process in itself), but to exclude the very cause of hepatotoxicity ?! Moreover, a number of NSAIDs are available for modern clinical practice, whose hepatotoxicity is minimal.

An extensive analytical report by J. Rubenstein et al. (2004), which is the result of a meta-analysis of 8 clinical studies of hepatotoxicity of NSAIDs, in addition to the established overall risk of clinically significant NSAID-induced liver damage in the population (4.8–8.6 / 100,000 patients per year), data on individual differences in hepatotoxic potential are presented. modern NSAIDs (Tables 1, 2) [43,50].

From the presented data, it follows that the greatest potential in terms of NSAID-induced hepatotoxicity is possessed by sulindac and indomethacin. Selective COX-2 inhibitor celecoxib and traditional NSAID naproxen have the lowest hepatotoxicity, based on the results of the studies. Confirmation that celecoxib is one of the least hepatoxic NSAIDs are the results of a meta-analysis of 14 multicenter studies conducted in Europe and North America and devoted to assessing the side effects of NSAIDs in patients with osteoarthritis and rheumatoid arthritis. At the same time, the frequency and severity of hepatotoxic effects of celecoxib (400 mg / day) were compared with those of naproxen (1000 mg / day), diclofenac (150 mg / day), ibuprofen (800 mg / day) or placebo during the course therapy lasting from 2 to 12 weeks (Table 3) [24,43,50].

The results of the meta-analysis indicate that the incidence of unwanted side effects from the liver (including serious) with celecoxib therapy does not differ from that with placebo and is significantly lower than with traditional NSAID therapy. Similar results were obtained when comparing the frequency of unwanted side effects of celecoxib, diclofenac and ibuprofen in the famous multicenter study CLASS (Celecoxib Long-term Arthritis Safety Study), which covered more than 8000 patients with osteoarthritis and rheumatoid arthritis. The incidence of undesirable side effects from the liver with diclofenac therapy was 4.7–5.3 times higher than with celecoxib or ibuprofen therapy. The difference in the incidence of undesirable liver side effects during therapy with celecoxib and ibuprfen was not significant [24,50].

According to modern concepts of syntropia, the anatomical and physiological unity of the hepatobiliary system and the gastrointestinal tract determines the development of diseases in the gastrointestinal tract in the presence of a pathological process in the liver and vice versa. Studies of the second half of the twentieth century have shown that among the causes of ulceration of the mucous membrane of the gastroduodenal zone, liver disease is one of the most significant factors along with chronic non-specific lung diseases and diseases of the cardiovascular system [1,3,7,8,12]. Screening of endoscopic examination in patients with chronic hepatitis and cirrhosis of the liver revealed the presence of acute or chronic ulcers in 52.2–75.0% of cases, while varicose veins of the esophagus and stomach were observed only in 40.0% of patients [12.19 , 32]. The formation of diffuse inflammatory-dystrophic liver diseases contributes to the development of pathological changes in the mucous membrane of the gastroduodenal zone long before the manifestation of hemocirculatory disorders. At the same time, the development of mucosal ulceration is equally pronounced in men and women and correlates in frequency with the degree of decompensation of liver functions in grades according to Child – Pugh [8,32].

G.V. Suporik and S.G. Kochetkov (2007), after conducting a targeted endoscopic examination of 125 patients with chronic diffuse liver diseases, found that all patients had a combined gastro-duodenal pathology. Almost all examined patients had an erosive lesion of the stomach, localized mainly in the antrum. The incidence of acute ulcers reached 10.5%, while ulcers were localized only in the stomach. Microscopically, in biopsy specimens of the mucous membrane, the phenomena of dystrophy of the surface and pit epithelium, atrophic changes in the fundic and antral glands, areas of necrosis in the mucous-submucosal layer were found [7]. According to F. Di Mario et al. (1998), in patients with chronic diffuse liver diseases, acute gastric ulcers were detected in 40.5% of cases, acute duodenal ulcers - in 48.6%, combined gastric and duodenal ulcers - in 10.9%. The author emphasizes that erosion and ulceration of the mucous membrane of the gastroduodenal zone occurs in almost all patients with portal hypertensive gastropathy [8].

Portal gastropathy (portal hypertensive gastropathy, PGG) is a term that reflects the state of the vessels of the submucosal layer and the mucous membrane of the gastroduodenal zone itself in conditions of portal hypertension (Fig. 2).

With PHG, multiple anastomoses are formed between the microvascular bed of the gastric mucosa, dilated veins, precapillaries of the stomach and esophagus. In conditions of portal hypertension, blood flow in the stomach wall increases, however, the gastric mucosa is in a state of chronic ischemia, which weakens the protective potential of the mucous membrane and predisposes to its damage. In the case of PHG, the use of the term “gastropathy”, according to most authors, is preferable to the use of the term “gastritis”, since the main morphological sign of PHG is epithelial and endothelial damage without inflammatory changes [1,7,8,32,47]. J. Krigeis (2005) indicates that bleeding from erosions of the mucous

membrane with PGH can account for up to 23% of all bleeding with cirrhosis of the liver [12]. It was noted that the frequency of PHG increases with the progression of diffuse liver diseases and closely correlates with the presence of esophageal and gastric varicose veins. Gastrointestinal bleeding caused by portal hypertension, as the cause of death in patients with liver cirrhosis, is in second place after bleeding caused by varicose veins of the esophagus and stomach. Bleeding in portal gastropathy leads to the development of anemia, which impairs liver function, and on the other hand, is a factor leading to the development of hepatic encephalopathy [3].

Considering the mechanisms of damage to the mucous membrane of the gastroduodenal zone in liver diseases, most authors use the concept of "Shay scales", which explains ulcerogenesis from the position of imbalance between the factors of aggression and defense factors. Obviously, the aggressiveness of the acid-peptic factor in liver diseases does not change, but the protective potential of the mucous membrane of the gastroduodenal zone is markedly reduced. The latter circumstance is a consequence of disturbances in hemoperfusion of the mucous-submucosal layer in both acute and chronic diffuse liver lesions. In the first case, the occurrence of acute liver failure leads to a reduction in visceral blood flow and the occurrence of typical ischemic damage to the gastroduodenal mucosa with the development of acute erosions and ulcers. In the case of chronic diffuse liver diseases, the development of stagnation in the portal vascular system significantly changes the volumetric blood flow rate in the microvasculature of all layers of the wall of the hollow organs of the digestive tract, especially in the area of localization of veins – anastomoses. Disturbances of microcirculation lead to the development of circulatory hypoxia with impaired transport of oxygen and energy substrates, edema of the paravasal interstitium. As a result, the regenerative potential of the mucous membrane is significantly reduced, which makes it possible to realize the damaging effect of the acid-peptic factor and leads to the development of erosive and ulcerative lesions in the gastroduodenal zone.

At the heart of NSAID-induced damage to the mucous membrane of the digestive tube is the inhibition of the synthesis of prostaglandins E2 and I2 (PgE2, PgI2) from arachidonic acid by traditional non-steroidal drugs by inhibiting the isoenzyme type 1 cyclooxygenase (COX-1). The effects of PgE1 include production of mucus adequate in terms of quantity and quality, secretion of bicarbonates into the gastric lumen, maintenance of sufficient volumetric blood flow in the mucous-submucosal layer, maintenance of mucosal repair by maintaining active proliferation of the cambial elements of the gastric epithelium. From this it follows that a natural consequence of therapy with traditional NSAIDs is a decrease in the protective potential of the mucous membrane of the digestive tract, which leads to the development of erosive and ulcerative lesions. According to the Shay scale concept, in this case, it is the decrease in the protective potential of the mucosa that leads to damage to the gastroduodenal mucosa against the background of a normal or hypoacid state. Acid-peptic effect in the formation of NSAID-induced erosions and ulcers plays the role of a producing factor [1,6].

An interesting fact is that vasoconstriction with hypoperfusion of the visceral and renal basins arising in acute liver failure caused by the toxic effect of NSAIDs by some authors is also associated with impaired prostaglandin synthesis under the action of the same NSAIDs [10,45,47]. In conditions of a decreasing effective volume of circulating blood in acute liver failure, the regional vasodilating effects of prostaglandins synthesized with the participation of constitutive COX-1 are especially important. Inhibition of prostaglandin synthesis by non-selective NSAIDs leads to an imbalance in the endothelin system (vasoconstriction) - prostaglandins (vasodilation) with the occurrence of prolonged ischemia. A

natural consequence of acute disorders of regional hemoperfusion are: the development of acute tubular necrosis and renal failure, the formation of foci of ischemic necrosis in the mucous-submucosal layer of the digestive tube with the occurrence of acute erosions and ulcers.

By combining the main links of the pathogenesis of NSAIDs - induced liver damage, accompanied by the development of acute or aggravated chronic liver failure, portal hypertension syndrome, resulting in damage to the mucous membrane of the digestive tract, as well as the immediate gastrotoxic potential of NSAIDs, it is not difficult to imagine a possible sequence of events, leading ultimately to the formation of acute erosive and ulcerative damage and the development of its complications: reduction of visceral arterial blood flow or chronic hypertension in the portal vein system, impaired hemoperfusion in the wall of the stomach and duodenum, ischemia and a decrease in the protective potential of the mucous membrane, the formation of erosions and ulcers under the influence of acid-peptic factor, the development of bleeding in conditions of deficiency of coagulation factors and hypocoagulation (Fig. 3, 4).

In conclusion, we consider it necessary to emphasize once again that the hepatotoxicity and gastrotoxicity of NSAIDs are pathogenetically interrelated processes. In contrast to the toxic effect of NSAIDs on the mucous membrane of the digestive tube, the mechanism of which has a clear and logical explanation, reasoning about the causes of the hepatotoxic effect of NSAIDs is currently very limited by our modest understanding of metabolic processes in hepatocytes. Nevertheless, it is absolutely unacceptable to explain the undesirable effects on the part of the liver during NSAID therapy by reactions of "idiosyncrasy", when hepatotoxicity is presented as a kind of exceptional and unpredictable phenomenon. Therefore, in the event of a sudden onset of painless jaundice, in addition to serological tests and ultrasound examination, it will be useful to clarify the patient's history and exclude drug damage to the liver, since many patients, thanks to widespread advertising, refer to some NSAIDs as food additives and do not consider it necessary to notify the attending physician about the use of non-steroidal drugs. If NSAID-induced liver damage is the most likely cause of liver failure, in addition to a number of standard measures in this situation, it will be useful to make sure that the mucous membrane of the gastroduodenal zone is intact. Nevertheless, given the extremely limited possibility of effective treatment of patients with acute liver failure, the only option for solving the problem of NSAID-induced hepatotoxicity (as well as in the case of NSAID-induced gastropathy), in principle, can only be targeted prevention of its occurrence, based on on the use of NSAIDs with minimal toxic potential.

Table 1. Risk of hepatotoxicity (laboratory criteria for hepatotoxicity ≥2N) with individual NSAIDs, controlled cohort study [G. Traversa et al., 2003]

Drug	Number of cases of hepatotoxicity per 100,000 patients per year (95% CI)	Relative risk of hepatotoxicity for a specific NSAID (95% CI)
Celecoxib	15,1 (0,4-84,2	1,0 (0,1-7,3)
Diclofenac	22,4 (9,7-44,1)	1,5 (0,7-3,2)
Ibuprofen	44,6 (5,4-160)	3,0 (0,7-12,4)
Naproxen	12,8 (0,3-71,1)	0,9 (0,1-6,2)

Nimesulide	33,1 (18,9-53,8)	2,2 (1,3-3,0)
Piroxicam	13,6 (4,9-46,4)	1,2 (0,4-3,4)

Table 2. The risk of a hepatotoxic effect (laboratory criteria for hepatotoxicity ≥2N) with the use of individual NSAIDs

Drug	Case (%) n = 107	Control (%) n = 248	Relative risk (unpaired ratio), CI 95%
Case-control study, taking into account the correspondence by gender, nationality, place of residence [J. Carson et al., 1993]			
Ibuprofen	3 (2,8)	9 (2,1)	1,3 (0,2-5,5)
Naproxen	1 (0,9)	7 (1,6)	0,6 (0,01-4,5)
Piroxicam	1 (0,9)	2 (0,5)	2 (0,03-38,0)
Sulindak	4 (3,7)	4 (0,9)	4,1 (0,8-22,4)
Case-control study, taking into account the correspondence by gender, nationality, place of residence [P.McCornic et al., 1999]			
Diclofenac	1 (2,8)	13 (2,6)	2,0 (0,2-17,4)
Ibuprofen	1 (2,8)	6 (1,2)	1,2 (0,1-12,0)
Indomethacin	4 (11,8)	30 (6,0)	2,6 (0,8-8,6)
Naproxen	3 (8,8)	27 (5,4)	1,7 (0,5-6,4)
Piroxicam	4 (11,8)	33 (6,6)	2,0 (0,6-0,8)
Sulindak	4 (11,8)	10 (2,0)	5,0 (1,3-18,5)

Table 3. Hepatotoxic side effects of NSAID therapy, results from a meta-analysis of 14 studies: celecoxib vs. placebo, celecoxib vs. traditional NSAIDs [24]

Side effects	Celecoxib (n = 3512) N (%)	Placebo (n= 1864) N (%)	Validity of differences (p)	Celecoxib (n = 3562) N (%)	Traditional NSAIDs (n = 2768) N (%)	Validity of differences (p)
All unwanted side effects						
Any side effects from the liver	28 (0,8)	17 (0,9)	>0,05 (unreliable)	32 (0,9)	53 (1,9)	<0.001 (authentically)
AsAT rise (> 2N)	14 (0,4)	8 (0,4)	>0,05 (unreliable)	8 (0,2)	22 (0,8)	0.001 (authentically)
Rise of ALAT (> 2N)			>0,05 (unreliable)	14 (0,4)	28 (1,0)	0.003 (authentically)
Serious unwanted side effects						
Any side effects from the liver	3(<0,1)	1 (<0,1)	>0,05 (unreliable)	4 (0,1)	10 (0.4)	0.05 (authentically)
AsAT rise (> 2N)	2(<0,1)	1 (<0,1)	>0,05 (unreliable)	2 (<0,1)	3 (0,1)	>0.05 (unreliable)
Rise of ALAT (> 2N)	3(<0,1)	1 (<0,1)	>0,05 (unreliable)	3 (<0,1)	5 (0,2)	>0.05 (unreliable)

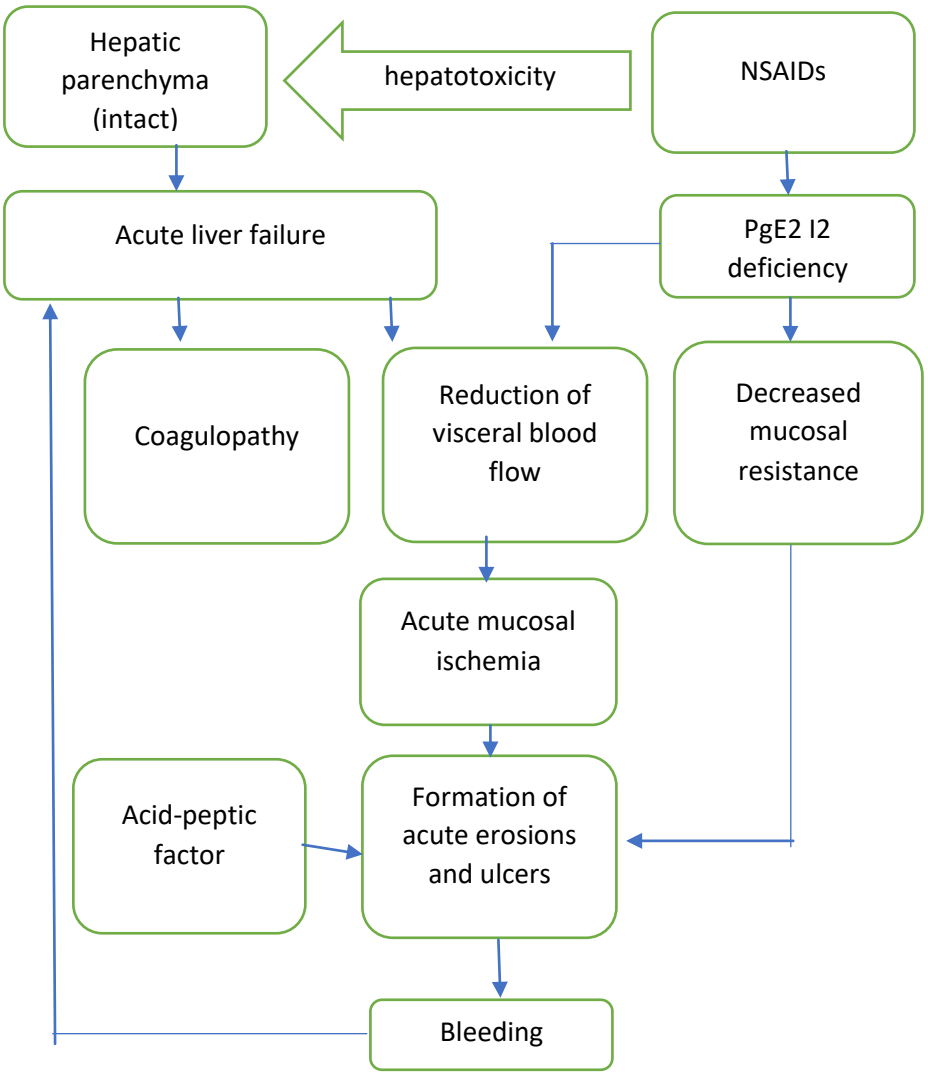

Fig 1. Interrelation of hepatotoxicity and gastrotoxicity of NSAIDs in chronic diffuse liver disease

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