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Disadvantageous effects of nonsteroidal anti-inflammatory drugs on the alimentary tract

Nonsteroidal anti-inflammatory drugs (NSAIDs) are the most frequently recommended pharmaceutical agents worldwide. About 70 mln prescriptions for these preparations are issued annually in the USA, over 20 mln in Great Britain. The situation is similar in the majority of European countries. However, these numbers do not show the real extent of the NSAID use, as they do not include the OTC (nonprescription) drugs, e.g. aspirin. It is estimated that about 1% of the American population uses NSAIDs every day.

These drugs are known to damage the gastric and duodenal mucous membrane. The injuries are usually severe – extravasation, intramucosal bleeding or erosions. They are not clinically significant as they are often asymptomatic (in 80% of patients) and do not indicate any possibilities of developing more serious mucous lesions; they are observed less frequently after prolonged administration of drugs due to adaptation.

A relevant clinical lesion of the mucous membrane is peptic ulcer, which is likely to be accompanied by bleeding or perforation. Recently, possible injuries to other parts of the alimentary tract, e.g. the esophagus, small and large intestine, were described (10). A substantial percentage of patients treated with NSAIDs report some alimentary disorders ranging from indigestion to spread abdominal pain. Some patients develop gastric or duodenal ulceration, alimentary bleeding, perforation. These severe adverse reactions may occur in patients without any complaints. And so the presence of dyspepsia in patients using NSAIDs is a useless indicator of complication risks since it does not correlate with the endoscopic picture of the stomach and duodenum and only in 25% of cases reflects organic lesions in the alimentary tract. Many patients with severe abdominal complaints show no abnormalities on endoscopic examination while those with large ulcers, perforation or bleeding do not suffer from any dyspeptic disorders prior to these complications.

Abdominal pain during the NSAID treatment is observed in about 10-12% of patients. It is estimated that about 5-15% of patients with rheumatoid diseases will have to discontinue their therapy due to severe complaints.

Severe complications are thought to develop in 1–2% of patients after the 3-month-treatment with NSAIDs and in 2–5% after the one-year use (9). 81% of patients who developed serious complications had no earlier prodramal symptoms (13). Most authors suggest that in patients treated with NSAIDs the risk of upper alimentary canal complications is 3–4 times higher compared to those who do not take these drugs. The most severe complications include: erosions, ulceration (developing in 1/3 of patients chronically treated with NSAIDs) accompanied by bleeding and perforation.

On endoscopic examinations, the patients treated with NSAIDs are likely to reveal submucous extravasation, erosion, ulceration. These lesions are mainly located in the prepyloric part of the stomach or duodenum (10). They occur in 5–30% of patients taking drugs for at least one month. The proportion of gastric to duodenal ulcers is 2:1 or 3:2 (11). The NSAID treatment delays ulceration healing and is the most serious factor resulting in ulcer insusceptibility to pharmaceutical and surgical treatment.

The *Helicobacter pylori* infections are estimated to develop in a similar percentage of patients, however eradication does not affect adverse reactions of NSAIDs to the process of ulcer healing.

The factors of increased risk of complications during NSAID therapy are well known. They are divided into certain and doubtful risk factors (3, 4, 5, 8, 12, 14, 15). The certain ones include:

1. Past ulcer or ulcer complications. The risk increases linearly with age.
2. Above 60 years of age. The elderly patients with ulceration or bleeding show 9% risk of severe complications using NSAIDs for 6 months.
3. Larger doses of NSAIDs. The change from small to medium or from medium to large doses doubles the risk of complications.
4. More toxic drugs, e.g. azopropazan, piroxicam, ketoprofen, tolmetin, indomethacin. The ratio of cyclooxygenase 2 (COX-2) to cycloogenase 1 (COX-1) inhibition correlates with the drug safety. The more active the drug towards COX-2 and less active towards COX-1, the safer it is for the gastric mucosa. Ibuprofen is thought to be the safest drug. Moreover, selective COX-2 inhibitors, e.g. celecoxyb are available and belong to the group of safe preparations.
5. Simultaneous steroid therapy. In the past steroids were suspected of resulting in ulcers in all patients, nowadays their use is not considered to be the risk factor in the whole population unless they are administered together with NSAIDs.
6. Simultaneous administration of anticoagulants. They mainly increase the risk of bleeding even from small ulcers or erosions.
7. Higher motor impairment in rheumatoid disease.
8. Coexisting cardiac and vascular diseases.

9. Simultaneous treatment with alkalating drugs since they create a false impression of increased safely. Decreased dyspeptic disorders or lack of them result in less cautions and prolonged use of NSAIDs. Nevertheless, the drugs have no protective anti-ulcerative effects and thus severe complications are likely to develop.

The doubtful complication risk factors include:

1. *Helicobacter pylori* infections. 2. Duration of NSAID treatment. Although it is believed that the length does not matter at all, it is also thought that the ulcer risk is present at any moment of this therapy. 3. Female sex. 4. Types of rheumatoid disease, e.g. the risk is higher in rheumatoid arthritis than in osteoarthritis. 5. Smoking. 6. Alcohol.

The injuries to the gastric and duodenal mucous membrane may result from local and systemic effects of NSAIDs. Due to the gastric acid, NSAIDs permeate through the gastric mucous barrier, get ionised and accumulate in the mucous membrane cells affecting them cytotoxically. Moreover, the local action destroys the mucous layers on the epithelial surface, which leads to impaired functions of the mucous barrier. However, this action is not the most important one as gastric ulceration also develops when NSAIDs are administrated parenterally or as coated tablets, which dissolve in the small intestine. Thus it should be remembered that parenteral NSAIDs do not show protective anti-ulcerative effects, although their unfavourable local action is avoided.

The major harmful effects are those related to inhibiting prostaglandins in the gastric wall due to COX-1 inhibition. Moreover, these drugs stimulate adhesion of neutrophils to the endothelial cells of fine vessels of the stomach and mesentary, which results in reduced capillary flow and ischaemia due to either capillary lumen obstruction or oxygen radical release. Another suggested mechanism is that of angiogenesis inhibition which would explain the NSAID effects inhibiting the healing process of already existing ulceration. NSAIDs impair also hemostasis decreasing the platelet activity which results from inhibiting the synthesis of thromboxan 2. This action increases the risk of bleeding from the alimentary canal (10).

The role of *Helicobacter pylori* in patients treated with NSAIDs remains controversial and has not been fully explained yet (2). There are some studies which show that *Helicobacter pylori* infections do not increase the risk of ulceration in patients treated chronically with NSAIDs (6). Other studies report that the lack of *Helicobacter pylori* eradication increases the risk of ulceration. Further studies are needed to explain more precisely the role of this infection as a risk factor in NSAID patients.

At present, eradication is rather not recommended in infected patients (with or without ulceration reported) treated with NSAIDs.

Similar findings concern adverse reactions of NSAIDs on the small intestine. Two types of injuries are distinguished (1). The first one includes the 2–3 mm-thick, diaphragm-like strictures forming numerous partitions. Such lesions result in no clinical signs and are usually diagnosed on autopsy (7). The second type of damage is called enteropathy and consists of increased permeability of the small intestine mucous mem-

brane, inflammatory changes similar to those observed in Leśniowski–Crohn's disease, micro-bleeding with subsequent anaemia and protein loss resulting in hypoalbuminaemia. The mechanisms implicated in these injuries are harmful effects of intestinal bacteria and bile as a carrier of NSAIDs in the hepatic-intestinal circulation (10).

The large intestine is also likely to be harmfully affected by NSAIDs. The drugs may cause spread inflammatory changes with erosions and ulceration similar to nonspecific inflammation (e.g. ulcerative colitis or Leśniowski–Crohn's disease). Moreover, the strictures similar to those observed in the small intestine may be found, which occur mainly in the right half of the colon. NSAIDs may exacerbate already existing diseases of the large intestine. The mechanism of toxic effects of these drugs on the large bowel is not fully known (10).

NSAIDs may also harmfully affect the esophagus resulting in inflammation, erosion, less frequently in ulceration or stenosis. These lesions are caused by damaging the mucous barrier and by inhibiting the secretion of bicarbonates. It should be stressed that the esophagus gets damaged by NSAIDs only when simultaneously exposed to acid action or when the doses used are very high.

Nonsteroidal anti-inflammatory drugs are common, effective analgesics, however, their use is related to a significant risk of alimentary canal complications. Since many patients in whom adverse reactions develop do not suffer from any complaints, before prescribing them one should take into account all possible harmful effects and identify the patients who are particularly at risk.

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SUMMARY

Nonsteroidal anti-inflammatory drugs (NSAIDs) are the most frequently recommended pharmaceutical agents worldwide. These drugs are known to damage the gastric and duodenal mucosa and also esophagus, small and large intestine mucosa. Severe complications are thought to develop in 1–2% patients after the 3-month treatment with NSAIDs. The most severe complications include erosions, ulceration accompanied by bleeding and perforation. These severe adverse reactions may occur in patients without any complaints. The factors of increased risk of complications during NSAIDs therapy are well known. The most important are: morbus ulcerosus disease, above 60 years of age, larger doses of NSAIDs, simultaneous steroid therapy, anticoagulants and *Helicobacter pylori* infection. NSAIDs may cause strictures and enteropathy in small intestine; and may exacerbate already existing diseases of the large bowel or also cause strictures. So, before NSAIDs prescribing one should take into account all possible harmful effects and identify the patients who are particularly at risk.

Niekorzystny wpływ niesteroidowych leków przeciwzapalnych na przewód pokarmowy

Niesteroidowe leki przeciwzapalne (NLPZ) należą do najczęściej zalecanych środków farmakologicznych na świecie. Powodują one uszkodzenia błony śluzowej żołądka, dwunastnicy, a także przełyku, jelita cienkiego i grubego. Ocenia się, że groźne powikłania zdarzają się u 1–2% pacjentów po 3-miesięcznym stosowaniu NLPZ. Najgroźniejsze powikłania to nadżerki, owrzodzenia wikłające się krwawieniem z przewodu pokarmowego, perforacją. Te poważne działania niepożądane mogą wystąpić u chorych, którzy nie odczuwają żadnych dolegliwości. Znane są powszechnie czynniki zwiększonego ryzyka powikłań stosowania NLPZ. Najważniejsze z nich to: choroba wrzodowa w przeszłości, wiek powyżej 60 lat, duża dawka NLPZ, jednoczesne stosowanie sterydów, antykoagulantów, infekcja *Helicobacter pylori*. W jelicie cienkim NLPZ mogą wywoływać zwężenia lub enteropatię, w jelicie grubym powodować zaostrzenie wcześniej istniejących chorób lub także mogą być przyczyną powstawania zwężeń. Podejmując decyzję o stosowaniu NLPZ, należy pamiętać o ich działaniach niekorzystnych i wiedzieć, którzy pacjenci są szczególnie zagrożeni.