ANNALES
UNIVERSITATIS MARIAE CURIE-SKŁODOWSKA
LUBLIN – POLONIA
VOL. LXII, N 1, 57 SECTIO D 2007

Rehabilitation Centre, Department of Clinical Endoscopy
Clinic of Internal and Occupational Diseases, Institute of Rural Medicine

TOMASZ SARAN, RAFAŁ STANISŁAW FILIP, KATARZYNA SODOLSKA, JANUSZ SCHABOWSKI

Concentration of nimesulid in gastric juice and blood after oral administration in combination with omeprazole

People suffering from joint complaints often take NSAIDs without medical control. As a result of availability 'without prescription' and patient's false conviction about low harmfulness of drugs of this group, a very great prevalence of adverse effects caused by NSAIDs is presently observed. Most often there occur symptoms on the part of the alimentary tract caused by lesions of the gastric mucosa of varying degrees, from asymptomatic to life threatening. Irrespective of the route of administration, NSAIDs cause a relative deficiency of PGE2 (7, 9) prostaglandin. This results in a decreased blood flow in the capillary vessels causing nutritional disorders, which make the maintenance of the integrity of the mucous barrier impossible (2, 4). When administered orally, NSAIDs not only decrease the systemic pool of PGE2, but in addition, exert a damaging local effect.

It was confirmed *in vitro* that high concentrations of NSAID cause direct activation of enzymes, oxidative phosphorylation disorders, disorders in fatty acids metabolism and in the transport of glucose (1, 3, 6, 8).

Modern NSAIDs are generally characterized by decreased acidity (pK_a of nimesulid is 6.5). Therefore, the effect of 'local harmfulness' of new generation drugs should be smaller. The presumption is logical that the strength of hazardous local effect of an individual drug depends on its penetration through the gastric mucosa and then release from gastric mucosa into the blood. According to the data from literature, after an oral administration nimesulid reaches its maximum concentration in plasma within 1.22 to 3.83 hours (5). The velocity of absorption is independent of the form of administration (tables, sachets, granules) and independent of the food consumed. Biological availability of oral forms exceeds 80%. Nearly 100% of the drug bonds the plasma proteins. The half-survival period in the body T1/2 remains within the range 1.80–4.75 hours. Nimesulid is subject to hepatic metabolism and excretion in 70% with urine and faeces. NSAIDs are currently often administered with the drugs of the proton pump inhibitors group, which decrease the amount of adverse effects on the part of the alimentary system.

The objective of the study was to determine the effect of simultaneous administration of omeprazole on the concentration of nimesulid – a non-steroid anti-inflammatory drug of new generation – in the gastric juice and whole blood after oral administration.

METHODS

Patients. The study was conducted among 34 volunteers of both genders (12 males and 22 females), aged from 24–70. People for the study were selected from among patients of the

Rehabilitation Ward at the Institute of Rural Medicine, hospitalized due to degenerative joint disease. Patients with indication for taking NSAIDs in order to alleviate pain complaints were qualified for the study. The patients were informed concerning the methods and objective of the study, also in a written form. The decision about participation in the study was confirmed by completing and signing the 'form of aware consent'. The following patients were not qualified for the study: 1) without indications for taking NSAIDs; 2) showing symptoms of diseases of the upper section of the alimentary tract or treated due to these diseases during the period of 12 months prior to the study; 3) showing symptoms of other serious diseases. Patients with mild arterial hypertension, obesity, lipid metabolism disorders, stable angina pectoris were not eliminated from the study; 4) taking NSAIDs or drugs affecting the secretion of the gastric juice within the period of 2 weeks prior to qualification.

Study procedure. Aulin, tablets containing 100 mg of nimesulid produced by Medicom International, Brno, were administered 120 min. after planned gastroscopy. Among people in the study, 19 patients were administered only a tablet of nimesulid, while 15 patients, apart from nimesulid, simultaneously received a gelatinous tablet containing 20 mg of omeprazole (Bioprazol produced by Biofarma, Poznań)

Collection of material. After insertion of a gastroscope through an emptied aspirating canal, the greatest possible amount of gastric contents was taken from the gastric lake to a dry container. Two specimens of the gastric mucosa were taken from the corpus and pylorus of the stomach in order to perform urease test. Venous blood was taken immediately after completing gastroscopy.

Preparation of material for analysis. Samples of full blood of the volume 3 ml defrosted at room temperature were subject to ultrasound homogenization by means of the Sonopuls UW 2070 homogenizator. From the homogenate obtained 200 µl was taken to a separate test probe and nimesulid was extracted by mechanical shaking for the period of 5 minutes in the presence of chloroform (6 ml). After centrifugation, the upper water layer was removed with a pipette. The remaining chloroform was transferred to a dry probe and evaporated at room temperature. The dry residue was dissolved in 100 µl of methanol and injected into the HPLC system at a volume of 20 µl. Defrosted gastric juice prior to extraction was centrifuged from the sediment and pH was obtained of approximately 7 by means of 1M NaOH solution. The standard were nimesulid solutions in full blood homogenate or gastric juice from 3 different patients who did not receive the drug.

Chromatographic analysis. Analysis was performed by means of liquid high pressure chromatography method consisting of: 1) gradient pump P580 (Dionex USA), 2) manual injector, loop 20 µl, 3) chromatographic column HR-80 Catecholamine (ESA, USA), 4) detector with diode matrix UVD 340S (Dionex, USA), 5) computer software Chromeleon v. 6.30.

The mobile phase consisted of acetonitril, water and phosphate buffer (triethylammonium phosphate Buffer Solution produced by Fluka). The flow of the mobile phase had a velocity of 2 ml/min. The contents of acetonitril in the mobile phase was from 0% at the beginning of the analysis to 70% after 11 minutes. The contents of phosphate buffer in mobile phase was 5%. The total flow time for one sample was 16 min. In these conditions nimesulid retention time was 10.5 min.

RESULTS

120 minutes after oral administration of a tablet of nimesulid the concentration of the drug in the gastric juice in all patients was ME=0.0043 (0.0009-0171) mg/ml. The concentration of nimesulid in whole blood was ME=0.0217 (0.0035 - 0.1078) mg/ml. The concentration of nimesulid in the blood was inversely proportional to the concentration in the gastric juice in individual patients examined (Fig. 1). The linear correlation ($y = -0.0503 x + 0.0064$) is statistical significant at $p<0.05$.

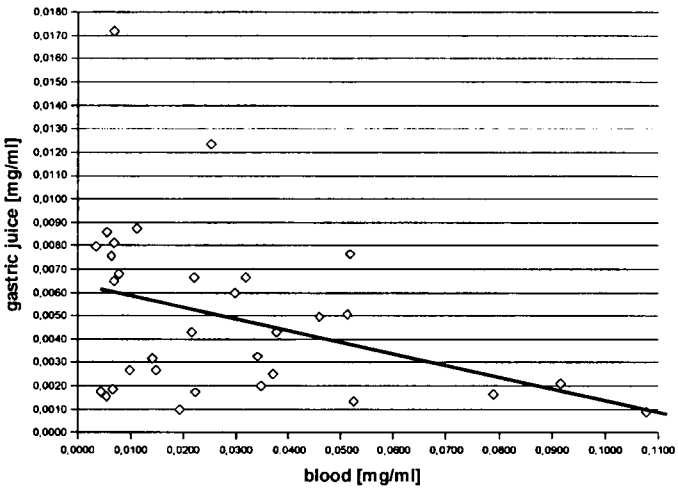

Fig. 1. Relationship between concentration of nimesulid in gastric juice and concentration in blood in individual patients in the study

In patients who received only nimesulid the concentration of the drug in the gastric juice was ME=0.0051 (0.0010 – 0.0171) mg/ml, whereas in patients who were administered nimesulid in combination with omeprazole the concentration was ME=0.0032 (0.0009 – 0.0123) mg/ml These values did not differed statistically. No statistically significant difference was noted between the level of nimesulid in full blood of patients who received nimesulid only, and those who were administered nimesulid with omeprazole. Median values were ME=0.0193 (0.0045 – 0.1078) and ME=0.0319 (0.0035 – 0.0877), respectively (Table 1).

Table 1. Nimesulid concentration in gastric juice and whole blood in patients who received tablets of nimesulid only and patients who received nimesulid in combination with omeprazole

	Nimesulid tablets 100mg administered orally median [mg/ml]	Nimesulid tablets 100mg and omeprazole capsules 20mg administered orally median [mg/ml]	Statistical significance Mann-Whitney test
Gastric juice	0.0051 (0.0010 – 0.0171)	0.0032 (0.0009 – 0.0123)	ns
Whole blood	0.0193 (0.0045 – 0.1078)	0.0319 (0.0035 – 0.0877)	ns

DISCUSSION

Within 120 minutes after oral administration of a tablet of nimesulid, the drug contained in it was dissolved into the gastric contents. The results obtained indicate that after this time nimesulid was nearly absorbed in most of patients and its concentration in whole blood exceeded by about 5 times the concentration in gastric juice.

While analysing the results for individual patients, a linear, negative relationship was observed between the concentration of the drug in the gastric contents and an its concentration in whole blood. The effect of simultaneous administration of omeprazole on nimesulid absorption from the alimentary

tract into the blood was not noted in our preliminary study. This was due to considerable individual dissimilarity in nimesulid concentrations in both groups of analysed patients.

REFERENCES

1. Garner A.: Mechanisms of action of aspirin on the gastric mucosa of the guinea pig. Acta Physiol. Scand. Suppl., 103, 101, 1978.
2. Hawkey C. J.: Nonsteroidal anti-inflammatory drug gastropathy. Gastroenterology, 119, 521, 2000.
3. Levi S. et al.: Inhibitory effect of non-steroidal anti-inflamatory drugs on mucosal cell proliferation associated with gastric ulcer bleeding. Lancet, 336, 841, 1990.
4. Miller T. A.: Protective effects of prostaglandins against gastric mucosal damage: current knowledge and proposed mechanisms. Am. J. Physiol., 245, 601, 1983.
5. Pieloch Z.: Nimesulid – a selective COX-2 inhibitor of special anti-inflammatory and protective properties with respect to articular cartilage. Prob. Ter. Monit., 12, 2, 2001.
6. Sanyal S. N. et al.: Effect of two non-steroidal anti-inflammatory drugs, aspirin and nimesulide on the D-glucose transport and disaccharide hydrolases in the intestinal brush border membrane. Pharmacol. Rep., 57, 833, 2005.
7. Sutherland L. R. et al.: A simple, non-invasive marker of gastric damage: sucrose permeability. Lancet, 343, 998, 1994.
8. Uribe A. et al.: Cell proliferation of the rate gastrointestinal mucosa after treatment with E2 prostaglandins and indomethacin. Digestion, 36, 238, 1987.
9. Vane J. R.: Inhibition of prostaglandin synthesis as a mechanism of action for aspirin-like drugs. Nature, 231, 232, 1971.
10. Zhu G. H. et al.: Nonsteroidal anti-inflammatory drugs could reverse *Helicobacter pylori* – induced apoptosis and proliferation in gastric epithelial cells. Dig. Dis. Sci., 43, 1957, 1998.

SUMMARY

Non-steroid anti-inflammatory drugs (NSAIDs) very frequently cause impairments of the gastric mucosa of varying degrees, from asymptomatic to those that are life threatening. After oral administration, NSAIDs exert an unfavourable systemic effect through the inhibition of prostaglandins and directly irritate the gastric mucosa. At present, NSAIDs are often administered in combination with drugs from the group of proton pump inhibitors. The objective of the study was determination of the concentration of nimesulid – a new generation of a non-steroid anti-inflammatory drug – in the gastric juice and whole blood after oral administration with omeprazole. The study covered 34 patients with recommendations for administration of NSAIDs due to pain complaints in the course of degenerative joint disease. Gastroscopy was performed 120 min. after oral administration of a nimesulid tablet (19) or nimesulid in combination with omeprazole (15). During gastroscopy, the whole gastric contents were taken from the gastric lake. A sample of gastric contents was centrifuged from the sediment and neutralized. After gastroscopy, venous blood was taken. Blood samples were then subject to ultrasound homogenization. Extraction of nimesulid from the samples of gastric juice and blood homogenate was performed with the use of chloroform. The concentration of nimesulid was determined by means of the high performance liquid chromatography system (HPLC) with diode array detector. In individual patients the concentration of nimesulid in the blood was inversely proportional to the concentration in the gastric juice ($Y=-0.05033x + 0.0064$, $p<0.05$). The concentration of

nimesulid in the gastric juice in patients who were administered nimesulid (ME=0.0051 mg/ml) did not significantly differ from the concentration in people who received nimesulid in combination with omeprazole (0.0032 mg/ml). The level of nimesulid in full blood was ME=0.0193 mg/ml and 0.0319 mg/ml, respectively; these values did not differ statistically. The results obtained show that 120 min. after an oral administration, nimesulid is absorbed or transferred, and is present in the gastric contents at a concentration over 5 times smaller than in full blood. Simultaneous administration of omeprazole does not significantly affect nimesulid absorption.

Stężenie nimesulidu w soku żołądkowym i surowicy po podaniu doustnym łącznie z omeprazolem

Niesteroidowe leki przeciwzapalne (NPLZ) niezwykle często powodują różnego stopnia uszkodzenia błony śluzowej przewodu pokarmowego, od bezobjawowych po zagrażające życiu. Po podaniu drogą doustną NPLZ wywierają niekorzystne działania systemowe za pośrednictwem zahamowania syntezy prostaglandyn oraz bezpośrednio drażnią błonę śluzową przewodu pokarmowego. NPLZ obecnie często są podawane wraz z lekami z grupy inhibitorów pompy protonowej. Celem badań było określenie stężenia nimesulidu – niesteroidowego leku przeciwzapalnego nowej generacji – w soku żołądkowym i we krwi po podaniu doustnym wraz z omeprazolem. W badaniach uczestniczyły 34 osoby ze wskazaniami do podawania NPLZ z powodu dolegliwości bólowych w przebiegu choroby zwyrodnieniowej stawów. Po upływie 120 minut od jednorazowego podania doustnego tabletki nimesulidu (19 osób) lub nimesulidu z omeprazolem (15 osób) wykonywano gastroskopię. Podczas gastroskopii pobierano całą zawartość treści z jeziorka żołądkowego. Próbkę treść żołądkowej odwirowywano z osadu i zobojętniano. Po gastroskopii pobierano krew żylną. Próbki krwi poddawano homogenizacji ultradźwiękowej. Ekstrakcję nimesulidu z próbek soku żołądkowego i homogenatu krwi wykonywano z użyciem chloroformu. Badanie stężenia nimesulidu przeprowadzano za pomocą systemu HPLC/UV. U poszczególnych badanych osób stężenie nimesulidu we krwi było odwrotnie proporcjonalne do stężenia w soku żołądkowym ($Y = -0{,}05033x + 0{,}0064$, $p<0{,}05$). Stężenie nimesulidu w soku żołądkowym u osób, które otrzymały nimesulid (ME=0.0051 mg/ml), nie różniło się istotnie od stężenia u osób, które otrzymały nimesulid i omeprazol (0,0032 mg/ml). Stężenie nimesulidu we krwi pełnej wynosiło odpowiednio ME=0,0193mg/ml i 0,0319 mg/ml, wartości te nie różniły się od siebie istotnie statystycznie. Uzyskane wyniki wskazują na to, że po upływie 120 minut od podania doustnego nimesulid ulega wchłonięciu bądź przemieszczeniu i występuje w treści żołądkowej w stężeniu ponad 5-krotnie mniejszym niż we krwi pełnej. Jednocześnie podawanie omeprazolu nie wpływa istotnie na wchłanianie niemesulidu.