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Effect of nimesulide – a preferential COX-2 inhibitor on arterial blood pressure, compared to ketoprofen

Arterial blood pressure is subject to instantaneous and long-term regulation. Instantaneous regulation malfunctioning leads to the development of arterial hypertension and is involved in the development of chronic hypertensive disease complications. Physiologic mechanisms responsible for the regulation of arterial blood pressure during longer periods of time are functionally associated with the activity of nephrons. In consequence, normally functioning mechanisms of renal regulation decide about the volume of circulating blood. The renal regulation of sodium excretion is provided by intrarenal and hormonal factors.

Among mechanisms regulating arterial blood pressure are the metabolites of arachidonic acid, which are produced with the presence of cyclooxygenase (COX). Among COX products within kidneys, prostaglandin E2 is dominant (PGE2). PGE2 exerts effect by means of four types of receptors associated with protein G: EP1, EP2, EP3 and EP4 (2). By means of these receptors PGE2 has a modulatory effect on hemodynamics and excretion of sodium and water (Fig.1). The distribution of the above-mentioned types of receptors within kidneys and their role is only poorly recognized. Receptors of EP1 type are present mainly within collecting tubuli, where their activation inhibits the resorption of sodium causing increased natriuresis. EP2 type receptors regulate the reactivity of the renal glomerule afferent vessels. In mice deprived of these receptors inborn arterial hypertension is observed. EP3 type receptors occur in afferent vessels, as well as in straight and collecting tubuli, where their activation has an effect opposite to that of vasopressin. Receptors of EP4 type are present within renal glomerule and collecting tubuli, and they probably regulate the tonus of renal glomerule, as well as the production of renin. Therefore, considering the regulation of the tonus of blood vessels within kidneys, PGE2 plays the role of a buffer by acting in two directions: angiospastic – through PE1 and PE2 receptors, and loosen – by means of PE3 and PE4 receptors.

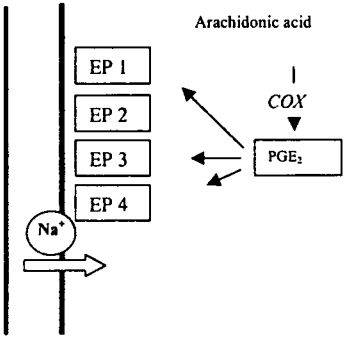

Fig. 1. The role of arachidonic acid metabolites in Na^+ excretion regulatory mechanism

Commonly applied non-steroid anti-inflammatory drugs are classified into COX inhibitors. The hypertensive effect occurring during the application of these drugs, and a considerable decrease in the effectiveness of drugs decreasing blood pressure in combined therapy has been known for a long time (9).

Nimesulide is a new generation non-steroid anti-inflammatory drug of non-typical chemical composition, characterised by the lack of carboxylic group, with the sulphonamide group (Fig. 2) (13, 15). Nimesulide is poorly soluble in water and is characterised by low acidity (acid dissociation constant pKa = 6.5). It is presumed that due to lower acidity of this non-steroid anti-inflammatory drug, its irritating effect on the alimentary tract mucus is relatively amaller. The anti-inflammatory, analgesic and antipyretic effect of nimesulide results from its capability for slight COX-1 inhibition and a stronger inhibition of COX-2. According to various researchers, the capability for COX-2 inhibition with relation to COX-1 is supposed to be 6 to 1,000 times higher. This difference in specificity explains a smaller hazardous effect of nimesulide of alimentary tract mucus (where the isoenzyme COX-2 is almost absent), with relation to the older generation of drugs. Unlike the celecoxib and rofecoxib which are much more COX-2- selective, nimesulide has not yet been subject to studies aimed at determination of its influence on the cardiovascular system, function of pellets and arterial hypertension. In addition, nimesulide shows an effect not associated with COX activity and non-specific for non-steroid anti-inflammatory drugs, which, however, may exert an effect on the function of the cardiovascular system.

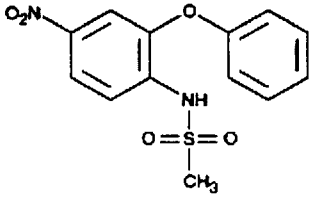

Fig. 2. Nimesulide N-(nitro-2-phenoxyphenyl)-methanesulphonamide

The effect of nimesulide – a preferential COX-2 inhibitor, was examined on mean values of arterial blood pressure in patients with hypertensive disease, compared to ketoprofen – a non-selective COX-1 and COX-2 inhibitor.

MATERIAL AND METHODS

The study covered 40 patients aged 18–65 hospitalised in the Clinic for Internal and Occupational Diseases and Rehabilitation Ward at the Institute of Agricultural Medicine. Patients were admitted to hospital due to arthrosis concomitant with idiopathic arterial hypertension. Patients with other serious diseases and those hospitalised due to high values of arterial blood pressure were excluded from the study.

Nimesulide (Aulin pills 100g, Medicom International, Brno, Czech Republic) were administered in a dose of 100 g in the morning and evening for 5 days. On the fifth day of administration of the drug 24-h arterial blood pressure monitoring was performed. During the subsequent 5 days, in the same patient, ketoprofen was administered (Profenid capsules 50 mg, Polfa, Cracow) in a dose of 50 mg 3 times daily and the monitoring of arterial blood pressure was repeated on the fifth day of treatment. Every second patient was administered the drugs in reverse order, i.e. first ketoprofen, then nimesulide (Fig. 2). Simultaneously, the patients were treated with drugs decreasing arterial blood pressure in mono-therapy and in combination.

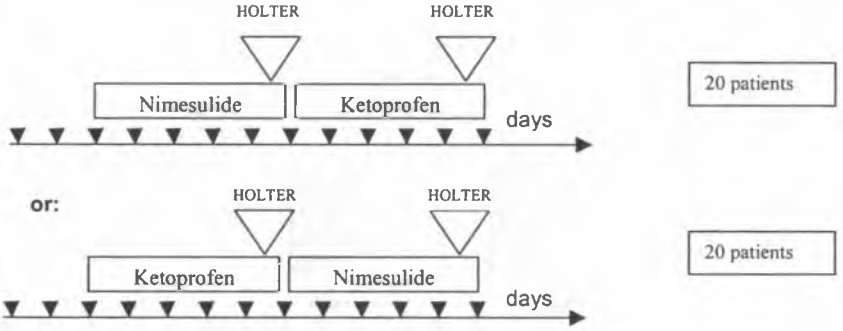

Fig. 3. Drugs administration and RR monitoring procedure during the study

A portable recorder with a Mobilograph-type arm cuff (Margot Medical, Warsaw) was used for the monitoring of arterial blood pressure. Measurements were performed automatically at 20-min intervals during the day (06:00 – 22:00) and at 30-minute intervals during the night. Preliminary calculations of the mean values were performed based on the computer software operating the recorder. The analysis covered daily records where the number of valid measurements exceeded 90%. Mean circadian arterial pressure, mean arterial pressure during the day and night were compared in therapies with nimesulide and ketoprofen. T-Student test and Chi^2 test were used contained in GraphPad Prism 2.0 software.

RESULTS

On the fifth day of administration of ketoprofen, the mean circadian arterial blood pressure was: systolic – 121.0 ± 2.5 mmHg, and diastolic – 74.5 ± 1.3 mmHg. In the same patients on the fifth day of treatment with nimesulide the mean circadian arterial blood pressure was: systolic – 119.8 ± 2.4 mmHg, and diastolic – 72.9 ± 1.0 mmHg (Fig. 4). These values did not differ statistically. Mean

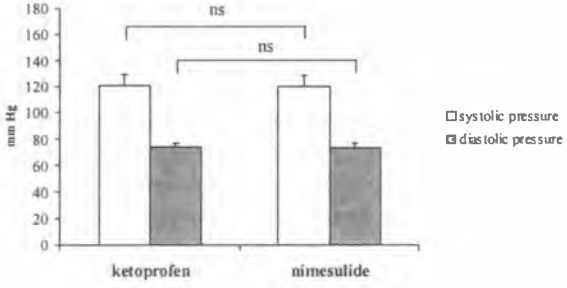

Fig. 4. Effect of ketoprofen and nimesulide therapy on systolic and diastolic 24-hour arterial blood pressure mean values

circadian arterial blood pressure during the day (06:00–22:00) in the course of treatment with ketoprofen was: systolic – 125.8 ± 2.3 mmHg, and diastolic – 77.6 ± 1.3 mmHg, whereas during treatment with nimesulide it was: systolic – 124.3 ± 2.3 mmHg, and diastolic – 75.8 ± 1.2 mmHg (Fig. 5). At night (22:00–06:00) mean arterial blood pressure during treatment with ketoprofen was: systolic - 110.1 ± 3.2 mmHg, and diastolic – 65.6 ± 1.6 mmHg, while for nimesulide: systolic – 108.6 ± 2.9 mmHg, and diastolic – 65.1 ± 1.3 mmHg (Fig. 6). In addition, within the range of circadian and nocturnal values of arterial blood pressure, no statistically significant differences were observed between measurements performed during treatment with nimesulide and ketoprofen.

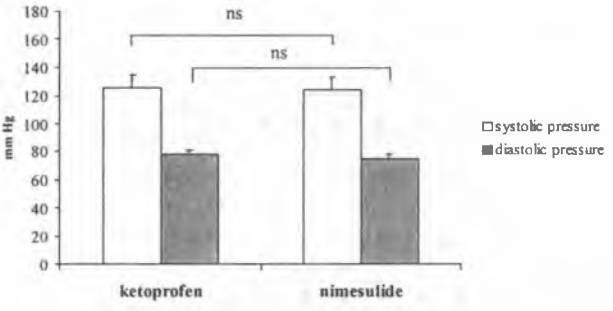

Fig. 5. Effects of ketoprofen and nimesulide therapy on systolic and diastolic day arterial blood pressure mean values

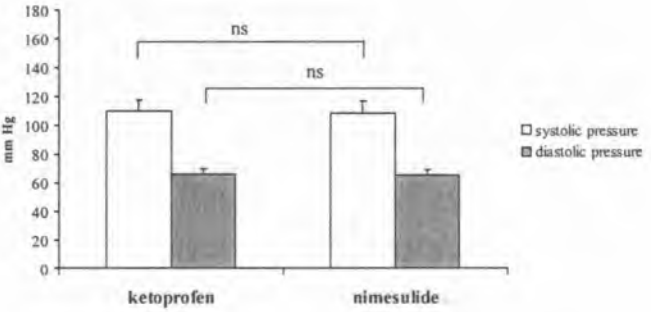

Fig. 6. Effects of ketoprofen and nimesulide therapy on systolic and diastolic night arterial blood pressure mean values

The percentage of measurements indicating an unsatisfactory control of arterial blood pressure during treatment with ketoprofen and nimesulide was also compared (Figs. 7 and 8). Values of systolic pressure exceeding 135 mmHg were noted in 8 mean circadian measurements during treatment with ketoprofen (20%), and in 5 mean circadian measurements during treatment with nimesulide (13%). Abnormal diastolic pressure (exceeding 85 mmHg) was observed in 5 mean measurements during treatment with ketoprofen (13%) and in 2 mean circadian measurements during treatment with nimesulide (5%). These values did not differ statistically.

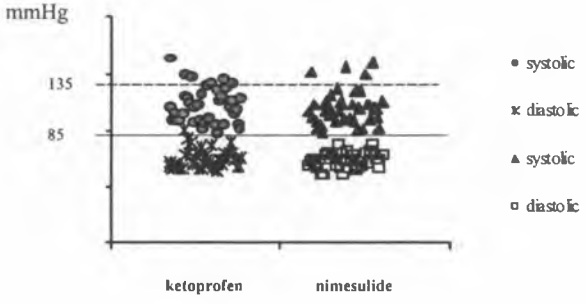

Fig. 7. Mean arterial blood pressure values in comparison to reference averages
--- systolic —diastolic

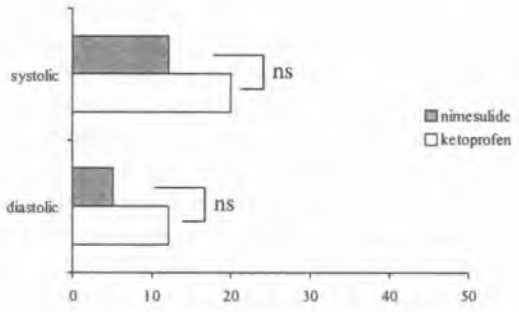

Fig. 8. The percentage of mean measurements indicating unsatisfactory control of arterial blood pressure

A decrease in arterial pressure at night by about 10% is a physiological phenomenon, which is eliminated in an insufficiently treated hypertensive disease. It was observed that the physiologic decrease in systolic and diastolic arterial blood pressure at night occurred in 24 patients (60%) during treatment with ketoprofen and in 27 patients (68%) during treatment with nimesulide (Fig. 9). These values did not significantly differ statistically.

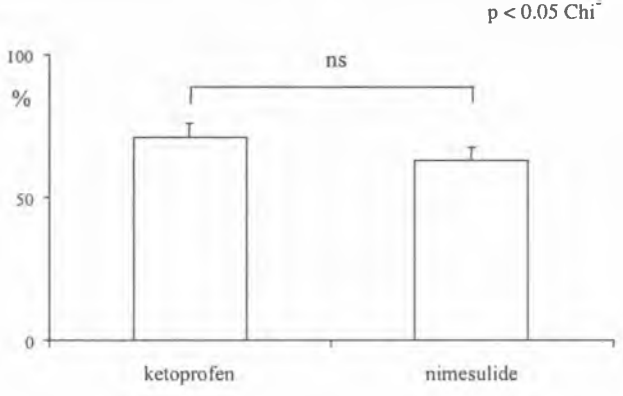

Fig. 9. The physiological decrease of arterial blood pressure at night (by 10% and over) during treatment

DISCUSSION

Non-steroid anti-inflammatory drugs of the older generation, which are non-selective with respect to COX, inhibit COX-1 enzyme to a greater degree than isoenzyme COX-2. As a result of treatment with ketoprofen in patients with arterial hypertension, a disregulation is noted which leads to an increase in mean values of arterial blood pressure during the 24 hour period (4). This often necessitates an increase in the doses of hypertensive drugs in order to maintain a satisfactory hypertension control. It is presumed that the main patomechanism of these unfavourable phenomena is an increased retention of sodium and water as a result of decreased PGE2 synthesis in the kidneys (1, 9).

The discovery of arachidonic acid cyclo-oxygenase isoenzymes, physiological forms (COX-1) and induced form (COX-2) in the 1990s of the 20th century raised hopes of avoiding complications in treatment

with non-steroid anti-inflammatory drugs (6, 7, 11). There occurred a period of increasing common use of selective COX-2 inhibitors. The researchers agree that selective COX-2 inhibitors cause clearly less undesirable effects with respect to gastric mucosa (3, 8, 16). The premise for the presumption about the possible superiority of selective drugs was the discovery of variations in the location of COX-1 and COX-2 within kidneys (10). It was observed that COX-1 isoenzyme is present mainly in the cells of the muscular coat of glomerural vessels, therefore its activity may more directly affect renal perfusion, while COX-2 enzyme is present in interstitial cells and cells of mesonephric tubuli. Unfortunately, many recent clinical and experimental studies did not confirm the anticipated superiority of typical selective COX-2 inhibitors (rofecoxib, celecoxib) over non-selective drugs with respect to benefits for patients with arterial hypertension concomitant with diseases of the osteoarticular system (4, 11, 14). Despite this, new drugs were considered to be safer, and in many European countries became dominant on the market over non--selective drugs of the older generation. Nimesulide is one of the most frequently applied non-steroid anti-inflammatory drugs. In some European countries, e.g. in Italy, it occupies the first position with respect to sales among non-steroid anti-inflammatory drugs (15).

Unlike drugs of the coxibs group, considered as more selective with respect to COX-2, nimesulide has not yet been the subject to comparative studies aimed at evaluation of its usefulness in patients with arterial hypertension, or other cardiovascular diseases.

The results obtained indicate the lack of superiority of nimesulide over ketoprofen considering the effect on circadian, nocturnal and diurnal mean values of arterial blood pressure. In addition, a smaller incidence of abnormally high mean circadian values of arterial blood pressure during treatment with nimesulide, compared to treatment with ketoprofen, was not confirmed. The studies were conducted in a comparative way, evaluating the reaction of each patient examined to both drugs at different periods of time. Due to this, the effect of individual susceptibility on results and conclusions was eliminated. The negative aspect of this method of conducting studies is the lack of 'placebo' group, therefore the effect of nimesulide itself on arterial hypertension cannot be evaluated with reference to the control group which did not receive analgesic drugs. The results of the studies, however, clearly indicate that nimesulide is not more desirable or safer than ketoprofen in the treatment of patients with arterial hypertension who require a simultaneous administration of non-steroid anti-inflammatory drugs.

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SUMMARY

Clinical and experimental studies have shown that renal and cardiovascular effects of most selective COX-2 inhibitors (rofecoxib, celecoxib) are similar to other traditional NSAIDs (dual COX inhibitors). In these study the effect of nimesulide – preferential COX-2 inhibitor, administration on 24-hour blood pressure profile was investigated in 40 adult individuals on antihypertensive therapy with pain states caused by osteoartritis. Nimesulide was administered orally, twice a day at the conventional dose of 0.1 g for five days. In the next (or previous) 5 days the same patients were administered with ketoprofen at the dose of 0.05 g three times a day. On the last day of the NSAID administration period, 24-hour blood pressure monitoring was performed. Our results indicate no difference between nimesulide and ketoprofen effects on mean blood pressure values during antihypertensive therapy.

Wpływ nimesulidu – wybiórczego inhibitora COX-2 na ciśnienie tętnicze w porównaniu z ketoprofenem

Badania kliniczne i eksperymentalne wykazały, że naczyniowo-sercowe efekty uboczne najbardziej selektywnych inhibitorów COX-2 (rofekoksyb, celekoksyb) są podobne do obserwowanych po tradycyjnych niesteroidowych lekach przeciwzapalnych. W przeprowadzonych badaniach oceniano wpływ nimesulidu – preferencyjnego inhibitora COX-2 na dobowy profil ciśnienia tętniczego u czterdziestu pacjentów leczonych z powodu nadciśnienia tętniczego oraz z powodu dolegliwości bólowych w przebiegu choroby zwyrodnieniowej stawów. Nimesulid podawano doustnie dwa razy dziennie w dawce 0,1g przez pięć dni. W ciągu następnych lub poprzedzających pięciu dni ci sami pacjenci otrzymywali ketoprofen doustnie w dawce 0,05 g trzy razy dziennie. W ostatnim dniu leczenia NPLZ przeprowadzono monitorowanie ciśnienia tętniczego. W wyniku przeprowadzonych badań nie stwierdzono różnicy pomiędzy nimesulidem a ketoprofenem w zakresie wpływu na dobowy profil ciśnienia tętniczego.