

Paracetamol phenomenon: unprecetended worldwide popularity vs. toxic effects

Jerzy Z. Nowak^{1,2}, Marta Jozwiak-Bebenista³

¹Institute of Pharmacology, Polish Academy of Sciences, Scientific Board, Krakow, Poland

²Medical Center MEDYCEUSZ, Bazarowa 9, PL-91-053 Lodz, Poland

³Department of Pharmacology, Medical University, Lodz, Poland

Author's address:

Jerzy Z. Nowak, Institute of Pharmacology, Polish Academy of Sciences, Scientific Board, Smetna 12, PL-31-343 Krakow, Poland; e-mail: jznowak07@gmail.com;

Received: 2013.12.09 • Accepted: 2013.12.13 • Published: 2013.12.20

Summary

Paracetamol (or Acetaminophen) is an analgesic and antipyretic drug known for many decades and widely used throughout the world. It is available without a prescription in mono- and multi-component preparations, recommended for children and adults. Although its therapeutic effectiveness is well established, there are still discussions on the mechanism/s underlying its biological activity. Obviously, it is complex as paracetamol affects many processes, including the effects on both the peripheral (COX inhibition), and central (COX, serotonergic descending neuronal pathway, L-arginine/NO pathway, cannabinoid system) antinociception processes and “redox” mechanism. Despite an array of biochemical actions paracetamol is a well tolerated drug and usually produces few side effects. However, due to its overuse every year, a steadily increasing number of registered cases of paracetamol-induced liver intoxication all over the world is reported. The growing problem of safety of paracetamol questions the validity of easy access to the drug occurring in being-in-sale preparations with different names, dosages, forms and various ingredients combinations. This paper surveys up-to-date concepts on paracetamol, its therapeutic applications and ways of action, with an emphasis put on the drug toxic effects, especially from the liver, as just hepatotoxicity creates an alarming problem of the paracetamol phenomenon.

Key words: paracetamol, acetaminophen, therapeutic applications, mechanism of action, toxic effects, hepatotoxicity.

Introduction

Paracetamol (an international name used in Europe) and **acetaminophen** (an international name used in the USA) are two official names of the same chemical compound derived from its chemical name: N-acetyl-para-aminophenol (the segment “cet” inserted between “para” and “amino”) and N-acetyl-para-aminophenol. This drug has a long history and as it often happens

with important discoveries it was found by chance. In the 80s of the 19th century, two young doctors at the University of Strasbourg in order to eradicate worms by mistake dispensed acetanilide to a patient instead of naphthalene (Fig. 1). They noticed that the drug had a small impact on intestinal parasites, however it significantly decreased high temperature. Young doctors – Arnold Chan and Paul Hepp – quickly

published their discovery and acetanilide was introduced into medical practice in 1886 under the name of antifebrin [15]. Soon it appeared that although the production of this drug was very cheap, acetanilide could not be used as an antipyretic medicament due to its high toxicity, of which the most alarming was methemoglobinemia. This resulted in a great deal of research on less toxic derivatives of acetanilide. Phenacetin and N-acetyl-p-aminophenol appeared to be the most satisfying compounds, which had been earlier synthesized by Harmon Northrop Morse in 1878 (Fig. 1) [47].

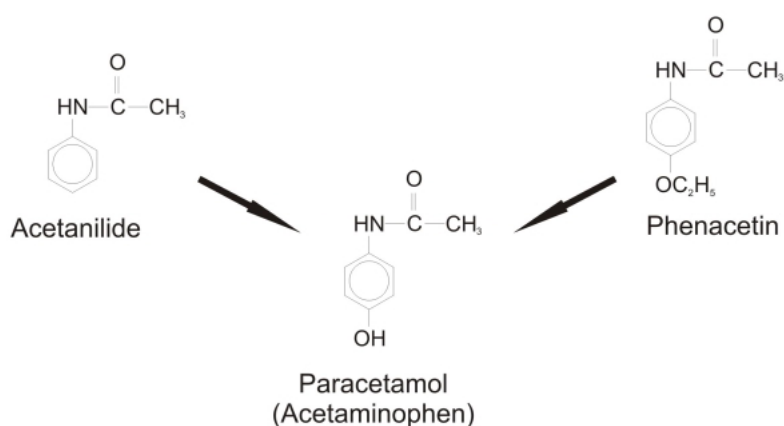


Figure 1: Chemical structure of analgesics – aniline derivatives.

Both acetanilide and phenacetin are metabolised to paracetamol (acetaminophen). Phenacetin until the 80s of the 20th century was included in the composition of numerous mixtures, e.g. Saridon (Roche).

Due to its carcinogenic action damaging the kidneys and the liver, as well as the patients' tendency towards an overuse of the drug, Saridon containing phenacetin was withdrawn from the American market in 1983; in the "new" Saridon, phenacetin was replaced by paracetamol. In the authors' country - Poland, and many other countries, it happened as late as in 2004.

The first clinical trials with those two acetanilide derivatives were performed by a German pharmacologist Joseph von Mering. On the basis of the obtained results, a faulty conclusion was drawn that paracetamol was characterised by high toxicity similar to acetanilide, therefore phenacetin was the first derivative to be introduced into medical practice in 1887. Phenacetin was widely used in analgesic APC (aspirin/phenacetin/caffeine) type mixtures until the time when it was associated with the development of analgesic nephropathy after a prolonged usage [75]. Acetaminophen/paracetamol became popular in fact half a year later when Bernard Brodie and Julius Axelrod demonstrated in 1948 that paracetamol was the main active metabolite of acetanilide and phenacetin responsible for their analgesic and antipyretic action and that methemoglobinemia was induced by another metabolite, i.e. phenylhydroxylamine [12]. That discovery revolutionised

the pharmaceutical market of analgesic drugs and since then paracetamol has started its staggering career.

The use of paracetamol

Paracetamol was introduced into the pharmacological market in 1955 by McNeil Laboratories as a prescribed analgesic and antipyretic drug for children under its trade name *Tylenol Children's Elixir* (the name tylenol derives from its chemical name – N-acetyl-p-aminophenol). One year later, 500 mg tablets of paracetamol were avail-

able over the counter (OTC) in Great Britain under the trade name *Panadol*, which were produced by Frederick Stearns & Co, the branch of Sterling Drug Inc. In the authors' country – Poland, paracetamol became available in 1961 and since then it has belonged to the one of the most frequently sold analgesic medications. There are, for example, about 100 preparations in the trade offer in Poland and possibly thousands or more in the world market, which contain paracetamol alone or in combination with other substance/s.

The paracetamol place on the WHO [World Health Organization] analgesic ladder, which defines the rules for application of analgesic drugs, is impressive. This drug has been placed on all three steps of pain treatment intensity. In different pains of moderate intensity, paracetamol as a weak analgesic together with non-steroidal analgesic drugs or co-analgesics (e.g. caffeine) is

a basic non-opioid analgesic (the first step of the analgesic ladder). When pain maintains or increases, paracetamol can be used as an additional analgesic with caffeine or weak (e.g. tramadol) or strong (e.g., morphine, phentanyl) opioids from the second and third step of the analgesic ladder, respectively). Paracetamol, if efficient, is a recommended oral analgesic of the first choice to be used for a long time, e.g. in symptomatic treatment of slight and moderate pain occurring in osteoarthritis, as well as in muscle or tendon pains. Moreover, it is a drug of choice in patients in whom application of non-steroidal anti-inflammatory drugs (NSAIDs) is contraindicated, e.g. in the case of gastric ulcers, hypersensitivity to aspirin, impairments in blood coagulation, in pregnant women, nursing mothers and children with fever accompanying a disease [44].

The use of paracetamol in children requires special care and maintain in an adequate dosage (based on age), which significantly differs from standard adult. The recommended dosage for children considers the metabolism of paracetamol, which determines the toxicity of the drug, especially hepatotoxicity (see below). In children paracetamol metabolism changes with age: in younger children the sulfation pathway is a dominated route of paracetamol elimination (which is mature at birth); the glucuronidation pathway takes about two years to mature. The oxidation of paracetamol, which takes place mainly with the participation of the enzyme CYP2E1 in neonates is negligible, because the activity of CYP2E1 increases with age, reaching the adult value at age 1-10 years. For comparison, in adults, paracetamol is metabolized mainly in the liver via glucuronidation (50%-60%), sulfation (25%-30%) and oxidation (< 10%) (see below in the section on adverse effects). Therefore, the currently proposed dosage of paracetamol in children up to 12 years is as follows [38]:

- under 2 years – no recommended dose; treatment under the supervision of a physician,
- 2-3 years – 160 mg (daily dose divided into two dose units, i.e. 2 x 80 mg); total dose corresponds to 1/2 of a single dose for an adult, i.e. 325 mg,¹⁾

- 4-6 years – 240 mg (daily dose divided into three dose units, i.e. 3x80 mg); total dose corresponds to 3/4 of a single dose for an adult,
- 6-9 years – 320 mg (daily dose divided into four dose units, i.e. 4x80 mg); total dose is the same as a single dose for an adult,
- 9-11 years – 320-400 mg (daily dose divided into four-five dose units, i.e. 4-5x80 mg; total dose corresponds to 1-1 1/4 of a single dose for an adult,
- 11-12 years – 320-480 mg (daily dose divided in the four-six dose units, i.e. 4-6x80 mg; total dose corresponds to 1-1 1/2 of a single dose for an adult.

Another paracetamol dosage schedule for pediatric patients recommended for example in the authors' country is as follows: 10-15 mg/kg b.w. oral dose and 15-20 mg/kg b.w. rectal dose every 4-6 h, maximum of 5 doses/day; in newborns orally or rectally 10 mg/kg of body weight every 4 hours or 15 mg/kg every 6 hours (maximum daily dose in newborns is 60 mg/kg b.w.).

Mechanism of action

Although paracetamol was discovered over 100 years ago and has been widely used in medical practice for more than half the century, its mechanism of action has not been elucidated until now [36]. It has analgesic and antipyretic properties similar to NSAIDs, but contrary to them, it does not possess any (or poor – see below) anti-inflammatory activity. When applied in recommended doses, it does not induce typical for NSAIDs gastrointestinal side effects. However, it suppresses prostaglandin production likewise NSAIDs.

Due to a lack of an anti-inflammatory component, paracetamol has not been regarded as a member of the NSAIDs family in pharmacological textbooks, although what is interesting, it has been always discussed together with these drugs. Therefore, the discussion on the mechanism of action of paracetamol should begin from the analysis of NSAIDs action.

¹⁾In the presented scheme, a single dose of paracetamol for an adult is 325 mg, which contrasts with still very popular 500 mg dose per tablet.

Nonsteroidal anti-inflammatory drugs (NSAIDs) and cyclooxygenase (COX)

All conventional NSAIDs inhibit the conversion of arachidonic acid (AA) into prostaglandin H – PGH₂. The stage is catalysed by prostaglandin H synthase (PGHS), at present referred to as cyclooxygenase (COX) within which isoenzymes COX-1 (PGHS-1) and COX-2 (PGHS-2) occur [30]. The prevalence and the role of the third isoenzyme COX-3 is the subject of ongoing to date discussions (read further). PGHS is a bifunctional enzyme and possesses two different enzymatic activities: cyclooxygenase and peroxidase (POX). The conversion of AA→PGH₂ involves two reactions: cyclisation of AA to unstable 15-hydroperoxide (PGG₂) with the involvement of a cyclooxygenase component and double oxidation in position 9 and 11; whereas the reduction of PGG₂ molecule to its 15-hydroxy-analogue, an unstable derivative of PGH₂, takes place due to peroxidase activity of PGHS (POX).

Prostaglandin H₂ (PGH₂) is a substrate for specific synthases, tissue-dependent isomerases, catalyzing its further conversions into different endogenous regulators, namely: prostaglandins of the D (PGD₂), E (PGE₂), F (PGF₂) series and prostacyclin (PGI₂; prostacyclin is not a prostaglandin and a commonly used abbreviation is historically conditioned) and thromboxanes (TXA₂ and TXB₂). They all are characterised by different biological activity and many of them have anti-inflammatory properties. Thus, the action of NSAIDs, which inhibit the stage of conversion AA→PGH₂, and also the formation of the aforementioned regulators, have some favourable effects, i.e. anti-inflammatory, analgesic and antipyretic, and side effects associated with the inhibition of synthesis of particular regulators in different tissues. A precise mechanism of NSAID action together with therapeutic and side effects has been presented in the recently published studies by the present author [51, 52].

Paracetamol and cyclooxygenases 1 and 2 (COX-1 and COX-2)

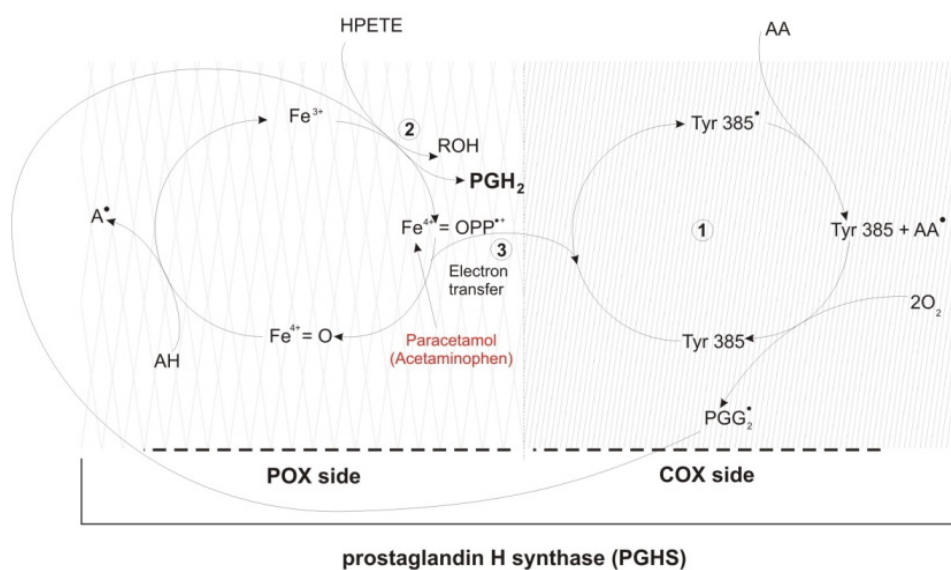
While traditional NSAIDs and selective COX-2 inhibitors inhibit cyclooxygenase (PGHS) through competing with arachidonic acid (AA) for the active site of the enzyme, [2] paracetamol is likely to act as a factor reducing a ferryl protoporphyrin IX

radical cation (Fe⁴⁺=OPP⁺) within the peroxidase site of the PGHS enzyme. In turn, the Fe⁴⁺=OPP⁺ generates tyrosine radicals in the place of PGHS cyclooxygenase, which are essential for catalysation of AA oxidation reaction [2, 3, 9, 32, 55] (Fig. 2). Due to the fact that hydroperoxides of fatty acids, like PGG₂ (reduced by POX) oxidize porphyrin within the peroxidase site of the enzyme, cyclooxygenase inhibition by paracetamol is difficult in the presence of high peroxide levels. Graham and Scott suggested that paracetamol should be classified to the group of the so-called atypical NSAIDs, determined as “peroxide sensitive analgesic and antipyretic drugs” (PSAAD) [25].

For the last decades, it was thought that paracetamol reveals analgesic and antipyretic properties by acting centrally and its inhibitory effect on COX-1 and COX-2 activity, i.e. prostaglandin synthesis, was rather low (when compared with NSAIDs). This concept was based on the original research carried out by Vane and colleagues which was published at the beginning of the 70s of the previous century. Those authors observed that paracetamol decreased prostaglandin synthesis ten times stronger in the brain than in the spleen [22].²⁾

²⁾In numerous academic textbooks including those published during the last decade, the central mechanism of paracetamol action has been discussed emphasizing its weaker inhibitory effect on the cyclooxygenase activity and prostaglandin production as compared to NSAIDs. The early study by Flower and Vane [22] published in the prestigious magazine *Nature* announced the mechanism of paracetamol activity even in its title: *Inhibition of prostaglandin synthetase in brain explains the antipyretic activity of paracetamol (4-acetamidophenol)*. Scientific prestige of the future Nobel's Prize winner (together with Sune K. Bergstrom and Bengt I. Samuelsson – “Nobel Prize” in 1982 in physiology and medicine for discoveries on prostaglandin and related biologically active substances) was so high that, despite later published articles which did not completely confirm the original results of the British researchers [42,70,73], this study was still cited and its results were considered the substantial basis of the mechanism of paracetamol action for many pharmacologists and doctors.

Flower and Vane [22] indicated that prostaglandin production in the brain was 10-fold more sensitive to paracetamol action than in the spleen. At that time, John R. Vane was the author of many other essential for medicine innovative observations that were published in prestige magazines, e.g. *Inhibition of prostaglandin synthesis as a mechanism of action for aspirin-like drugs* [74]. John R. Vane, using a guinea pig lung homogenate in his study, concluded that analgesic, antipyretic and anti-inflammatory action of aspirin, indomethacin and salicylate is associated with a lower prostaglandin production resulting from cyclooxygenase inhibition (COX). Other articles published in the

**Figure 2:**

The complex of prostaglandin H synthase (PGHS), including two components: cyclooxygenase (COX) and hydroperoxidase (POX), is a bifunctional enzyme responsible for the metabolism of arachidonic acid (AA) to prostaglandin PGH₂. The reaction occurs via two stages:

1. AA oxidation to PGG₂ depends on tyrosine radical (Tyr385^{*}) in the COX site;
2. PGG₂ undergoes reduction to PGH₂ in the POX site, which results in the oxidation of the peroxidase heme radical;
3. A formed ferryl protoporphyrin IX radical cation (Fe⁴⁺=OPP⁺) generates Tyr385^{*} radicals. Thus, the POX part is "self-sufficient", whereas COX depends on POX. Paracetamol reduces an iron cation in protoporphyrin IX radical (Fe⁴⁺=OPP⁺) in the POX part, which contributes to a lower amount of Tyr385^{*} radical formation.

Explanation of abbreviations: AA – arachidonic acid; AA^{*} – arachidonic acid radical; A^{*} – oxidized cosubstrate; AH – reduced cosubstrate; Fe³⁺ – enzyme at rest; Fe⁴⁺=O – protoporphyrin IX (haem); Fe⁴⁺=OPP⁺ – protoporphyrin radical IX; HPETE – hydroperoxides of fatty acids; PGG₂^{*} – prostaglandin G₂ containing peroxide radical; PGH₂ – prostaglandin H; ROH – alcohol; Tyr385^{*} – tyrosine radical

Paracetamol and cyclooxygenase-3 (COX-3)

At the time of pioneering discoveries made by John R Vane in the early 70. last century, COX isoforms were not known because isoenzyme COX-2 was identified only at the beginning of the 90s of the previous century [24, 76]. Ten years later, the experiments performed on the dog's brain tissue revealed the presence of the third COX isoform, COX-3, which demonstrated unexpected high sensitivity to paracetamol [17]. However, it soon appeared that so sensitive to paracetamol COX-3 does not function in the human organism. The human analogue of dog's COX-3, which occurs in some tissues especially of the central nervous system, is an alternative splice variant of COX-1 without a preferential sensitivity to paracetamol, encoding proteins of amino acid sequence different from COX and not exhibiting COX activity [20, 41, 65]. Thus, COX-3 involve-

same magazine *Nature* by Ferreira *et al.* *Indomethacin and aspirin abolish prostaglandin release from spleen* [21] and by Smith and Willis *Aspirin selectively inhibits prostaglandin production in human platelets* [67] contained the results confirming those observations. It is worth remembering that COX isoenzymes were not discovered at that time.

ment in the mechanism of action of paracetamol in humans has not been justified, which has been confirmed by Kis *et al.* [41] as well as by Hinz and Brune [32]. However, the discussions regarding a potential role of identified three COX isoenzymes in the mechanism of paracetamol action are still being continued [5,10,11,63].

The concept regarding COX-dependent central mechanism of paracetamol action has not stood the test of time [41]. Firstly, the studies by Graham and Scott [26] have shown that paracetamol really inhibited prostaglandin synthesis in well-functioning cells, however it did not exert the same effect in the tissue/cell homogenate, where the concentration of arachidonic acid is low. Secondly, paracetamol has been found to have an inhibitory impact on COX-1 and COX-2 activity in peripheral tissues, although not to the same extent, since a stronger effect was always observed in relation to COX-2, especially in the cells of the vascular endothelium. Hinz *et al.* [33] indicated that orally administered paracetamol at a dose of 1 g inhibited 80% of the COX-2 activity in human blood monocytes. The results of extensive studies by Hinz and Brune published in the years

2006-2012 revealed that paracetamol is a preferential inhibitor of COX-2 isoenzyme, however its effect depends to a great extent on the state of environmental oxidation/reduction (redox) [32,34].

Paracetamol and serotonergic pathways

Among other possibilities of the central action of paracetamol, its stimulating effect on descending serotonergic pathways which are involved in inhibition of pain sensations has been discussed. This theory has been confirmed by *in vivo* studies on animals as well as on humans. Alloui *et al.* [1] carried out the study on analgesic and anti-inflammatory action of paracetamol in rats which were given caragenin. No anti-inflammatory effect of paracetamol was observed, however central antinociceptive effect of this drug with the involvement of the 5-HT₃ subtype of serotonin receptors was detected. The study on healthy volunteers in whom the pain was induced through electrical stimulation of the median nerve showed that analgesic action of paracetamol was completely blocked in the group of subjects treated with paracetamol combined with tropisetron or granisetron (5-HT₃ receptor antagonists) [58,59]. Data concerning central action of paracetamol through its effect on descending serotonergic pathways do not exclude a hypothesis assuming the presence (or coexistence) of the inhibition of prostaglandin synthesis [26]. Prostaglandin PGE₂ modulates numerous physiological processes and can also modulate nociceptive and autonomic processes via its influence on descending serotonergic antinociceptive system [50].

Paracetamol and endocannabinoid system

Novel studies on the mechanism of action of paracetamol regard it as a pro-drug, which due to its active metabolites demonstrates an association with the endocannabinoid system. It has been observed that in mouse brain and spinal cord, paracetamol is subject to deacetylation to p-aminophenol that in turn reacts with arachidonic acid affected by fatty acid amide hydrolase (FAAH) resulting in the formation of an active metabolite of the drug, the fatty acid amide N-arachidonoylphenolamine (AM404) [37,54]. AM404 does not act directly on cannabinoid receptors, however, it increases activity of endocannabinoid system in an indirect way [40]. On one hand, this

compound is a strong activator of the vanilloid receptor type 1 (TRPV1), being a ligand of receptors for cannabinoids CB1, and on the other hand, it leads to an increase in the endogenous pool of these compounds as an inhibitor of the endogenous cannabinoid (anandamide) reuptake [77]. Endogenous cannabinoids, e.g. anandamide, act antinociceptively both at the level of the spinal cord as well as the brain.

The study on rats performed by Bertolini *et al.* [6] presented that an earlier administration of the CB1 receptor antagonist inhibited AM404 activity and completely blocked analgesic action of paracetamol in these animals. Moreover, cannabinoids considerably lower body temperature through the activation of CB1 receptors in the pre-optic area [56]. It has been known that analgesic derivatives of aniline have a similar action as cannabinoids, such as mood improvement, psychic relaxation and sedation. Such properties have not been observed so far in the case of paracetamol, although some authors ascribe poor sedative properties to it [4,41]. Furthermore, different concentrations of AM404 have been found to inhibit COX-1 and COX-2 enzymes. This mechanism may be important especially in such areas of the brain in which a high concentration of FAAH enzyme can be observed, e.g. in the mesencephalic trigeminal nucleus, primary sensory neurons. In these areas of the brain an increased production of the active metabolite AM404 can be found, and this in turn may to a certain degree explain the inhibitory action of paracetamol towards cyclooxygenases in the CNS [6].

Paracetamol and nitrogen oxide (NO) pathway

Inhibition of nitrogen oxide (NO) formation might be also an alternative (or an additional) mechanism of analgesic action of paracetamol. The L-arginin/NO pathway activated by substance P and NMDA receptors leads to NO synthesis, which is an important neurotransmitter in the nociceptive processes of the spinal cord [7, 14].

Conclusions

Paracetamol acts at all levels of pain stimulus conduction from the tissue receptors through the spinal cord to the thalamus and the cerebral cortex in which pain sensations are evoked. The

mechanism of analgesic action of paracetamol is complex. The following possibilities are still taken into consideration: affecting both peripheral (inhibition of COX activity) and central (COX, descending serotonergic pathways, L-arginin/NO pathway, cannabinoid system) antinociceptive processes as well as the redox mechanism [66]. The studies on the mechanism of paracetamol action require further verification – they should concern not only the therapeutic action of this drug but also more frequently reported poisoning, especially strong hepatotoxicity, resulting from the drug overdose since numerous preparations containing paracetamol, are available without a prescription.

Paracetamol on the pharmaceutical market

Paracetamol is available on the market under different trade names in simple (sold over the counter – OTC) or more complex preparations combined with an additional active substance or substances obtainable only by prescription (with tramadol) or without it (in combination with codeine phosphate, ascorbic acid or diphenhydramine hydrochloride, as well as NSAIDs such as ibuprofen or propyphenazone). Paracetamol occurs in the form of tablets, effervescent tablets, suspension, powder to prepare oral liquid medicine (sachets) and rectal suppositories. When administered orally clinical effect of paracetamol appears after 30 min. Paracetamol content in oral medicaments differs; most frequently it equals 500 mg, however there are preparations (most often complex) which contain 325 mg of paracetamol or 750 mg (e.g. Febrisan, Coldrex) or even 1000 mg (e.g. Efferalgan Forte, Coldrex MaxGrip, Flucontrol Hot). The fastest action of paracetamol, seen already after 15 min, occurs in the case of using fast-release tablets, enriched with sodium bicarbonate which enhances stomach emptying. Due to this process, paracetamol passes quicker to the small intestine where it undergoes absorption (e.g. Panadol Rapid®).

Interestingly, when administered rectally (suppositories), bioavailability of paracetamol is lower, about two thirds of availability as compared to oral administration. The time necessary to achieve the therapeutic concentration for

suppositories is 120-180 min, which means that analgesic action occurs after 2–3 h since the drug intake. Bioavailability and speed of absorption of paracetamol in the form of suppositories depend on numerous factors: the drug dose (in adults usually 650 mg; in children 80-325 mg), the size of the suppository (the smaller and the lower dose the better bioavailability is), the type of vehicle (the higher vehicle lipophilicity, the greater bioavailability and the faster effect but the shorter time of drug action) and the degree of rectal vascularisation. Slower absorption of paracetamol applied via rectum (suppositories) differs from other analgesic medicaments: e.g. sodium diclophenac in the form of suppositories in the preparations such as e.g. Dicloberl (50 mg of the active substance) or Dicloratio (25, 50 and 100 mg) achieves the maximal blood concentration after 30 min since the application, in the preparations: e.g. Diclac and Diclofenac GSK (50 or 100 mg) or Voltaren (25, 50, 100 mg) – after 60 min, and in Olfen (50 and 100 mg) – after 2 h (data according to Pharmindex 2012 – Polish edition). These data show that the speed of absorption of an active substance from the drug administered *per rectum* (affecting the occurrence of the therapeutic effect) is influenced by the form and composition of the adjuvant substances contained in suppositories; the same factors affect the suppositories containing paracetamol. Slower absorption of the drug is usually associated with its longer presence in the organism, i.e. with a longer time of action, which in the case of pain complaints is of considerable importance.

Paracetamol can be also used intravenously (i.v.) and therefore is widely used in the hospital health service, e.g. in the postoperative pain therapy (it has been evidenced that the administration of paracetamol especially during the first hour of treatment is more efficient in reducing pain intensity than given orally), in order to quickly decrease high fever or in the case when another route of administration is not possible [46, 57]. At the beginning, propacetamol – precursor of paracetamol (Pro-Dafalgan®, Bristol-Myers Squibb; Pro-Efferalgan, UPSA) was used which after the i.v. administration underwent hydrolysis to paracetamol and diethylglycine under the influence of plasma esterases. In 2005, an intravenous form of a new generation paracetamol was registered as a solution ready to be infused at the concentration of 500 mg/50 ml or 1 g/100 ml

(Perfalgan®, Bristol-Myers Squibb) which completely removed pro-paracetamol (propacetamol) from medical practice [57, 71].

Side effects – toxicity of paracetamol

When appropriate dosage of medicaments containing paracetamol is used, i.e. maximum dose of 4 g/24 h, usually no serious side effects have been observed, besides possible allergic skin reactions, although after higher doses or prolonged duration of taking the drug, some side effects may occur, especially in the liver (Table 1) [27].

Adverse Event Reporting System) collected during the period from October to December 2012. The preparations containing paracetamol will be evaluated in terms of the drug-induced adverse skin reactions.

After ingestion of paracetamol, about 90% of the compound undergoes metabolism in the liver by conjugation with glucuronic acid (50-60%), sulphuric acid (25-35%) and cystine (approximately 3%) to form pharmacologically inactive metabolites, which are eliminated with urine. A small amount of the drug (about 5%) is eliminated in an unchanged form by kidneys. Subsequent 5% of

Table 1: Advantages and disadvantages of paracetamol therapy

Advantages (when the drug is administered in the recommended therapeutic doses max. 4 g/24 h)
wide therapeutic application
checked and examined
well tolerated
good bioavailability after oral administration (t _{1/2} 2h)
fast elimination
cheap
a small number of interactions with other drugs
low toxicity to the digestive tract and kidneys when used at low doses (≤ 2 g / d)
low toxicity in children
rare side effects (main allergic skin reactions) available in different pharmaceutical forms
Disadvantages
metabolised to a toxic metabolite (N-acetyl-p-benzoquinone imine).
therapeutic index (often not efficient at a low dose)
long-term application may cause: <ul style="list-style-type: none"> • renal functioning disorder • higher blood pressure • increased prevalence of heart infarction
low therapeutic efficiency <ul style="list-style-type: none"> • analgesic action at a dose of 1 g administered 2, 3, and 4 times a day • low anti-inflammatory action
hepatotoxicity <ul style="list-style-type: none"> • increased aminotransferase activity at therapeutic doses • hepatic failure in the case of overuse (two-fold overuse of a therapeutic dose) • enhanced previous liver damage caused by alcohol consumption • combinations with traditional NSAIDs can result in a higher prevalence of digestive tract ulceration

Interestingly, at the beginning of this year, the US FDA introduced paracetamol on the list of the preparations, which will undergo specific monitoring on the basis of information from the system on adverse reactions (FEARS, the FDA

paracetamol is subject to N-hydroxylation in the liver with the involvement of cytochrome P450 enzymes (particularly CYP2E1) to form a toxic metabolite N-acetyl-p-benzoquinone imine (NAPQI), which is very rapidly inactivated by

glutathione sulfhydryl groups and excreted with urine as mercapturic acid [6].

Severe liver impairment after paracetamol overdose was documented for the first time in Great Britain in 1966 [19]. Since then, a steady increase in the number of accidental or intended poisonings has been noted all over the world. The main cause of this situation is a huge amount of preparations containing paracetamol, which are available OTC on the pharmaceutical market, i.e. without any prescription (for example in the authors' country, the number of such preparations currently reaches 92 items, including 39 single and 53 complex products). Depletion of hepatic glutathione stores occurs as a result of an intensive metabolism following intentional and unintentional overdose of paracetamol (ingestion of more than 4 g/24 h, i.e. over 8 tablets, 500 mg each!). In such a situation, paracetamol becomes a dangerous and life-threatening drug because the formed highly reactive NAPQI metabolite covalently binds to hepatocyte macromolecules leading to impoverishment of enzymatic systems and structural and metabolic damage to the liver (potential lethal hepatic necrosis). In the later stage of poisoning, renal tubular necrosis and hypoglycemic coma may appear [48]. It is worth mentioning that the weakened hepatic function (caused by slimming, malnutrition, hepatitis C virus – HCV, human immunodeficiency virus – HIV), alcohol overuse or application of paracetamol combined with drugs inducing cytochrome P450 (e.g. rifampicin, barbiturates, carbamazepine) can lead to hepatic impairment much easier, even when the compound is used in therapeutic doses. Development of acute hepatic failure as a result of paracetamol overuse (i.e. 7.5–15 g /24 h) as well as the methods of its treatment have been precisely discussed in many studies for the last ten years [6, 45, 68, 72]. The authors of the present study concentrate on other (likely to be potential) adverse reactions of paracetamol, which result from its mechanism of action.

Results of recent reports on paracetamol as a peripheral selective COX-2 inhibitor encourage researchers to analyse this drug more critically. The question arises as to whether paracetamol revealing a similar pharmacological profile to

coxibs may induce the same side effects, especially when the drug is used for a long time.³⁾ A permanent blockade of prostaglandin synthesis through selective COX-2 inhibitors is currently regarded as a cause of adverse cardiovascular reactions in patients after a prolonged use of these drugs [18,32-34]. Long-lasting COX-2 inhibition decreases the production of vasoprotective prostacyclin (PGI₂) by vascular endothelial cells, which inhibits platelet aggregation and has vasodilatory capacity. This impairs the balance between thromboxane and prostacyclin and causes thrombus formation. Contrary to the inflammatory tissue, the endothelial cells possess a low level of peroxides, so they are not likely to inhibit paracetamol activity against COX-2 [9].

It has been shown that oral administration of paracetamol at the dose of 500 mg decreases the amount of excreted with urine 2,3-dinor-6-keto PGF_{1α}, the main stable inactive metabolite of prostacyclin, whose synthesis is mediated by endothelial COX-2 [28]. Likewise, 50% reduction in this metabolite excretion in the urine of pregnant women was noted after ingestion of 1 g of paracetamol [53]. Taking into consideration aforementioned results obtained by Hinz *et al.* [33] regarding over 80% inhibition of COX-2 in the vascular endothelium caused by paracetamol it can be speculated that such a mechanism of action would be responsible for adverse cardiovascular reactions in patients who take this drug regularly. It should be emphasized that paracetamol due to its short half-life (approximately 2 h) induces a short-lasting inhibition of COX-2 activity.

Thus, in order to eliminate pain it is necessary to administer repeated 1 g doses of paracetamol

³⁾Coxibs, NSAIDs selectively inhibiting COX-2 activity, do not affect (in therapeutic doses) COX-1 at the same time. Due to such a mechanism of coxibs' activity, their side effect on the digestive system, which happens in the case of traditional NSAIDs, was eliminated. However, later clinical observations indicated that patients using coxibs for a long time developed adverse cardiovascular reactions. Thus, because of a higher risk of such perturbations in those patients, coxibs (etoricoxib, lumiracoxib, rofecoxib and valdecoxib) have been withdrawn from sale. Rofecoxib known under the trade name of Vioxx (Merck & Co.) was withdrawn as the first one in 2004 after the 5-year existence on the pharmaceutical market; valdecoxib (Bextra, Pfizer) was the next drug withdrawn in 2005. At present only one drug of this type, celecoxib (Celebrex Pfizer Europe) is available for therapy.

for maintaining constant (80%) inhibition of COX-2. This fact has to be considered by a doctor prior to making the decision about long-term treatment with paracetamol in order to avoid the drug overdose.

Epidemiological data reveal that long-lasting administration of paracetamol affects blood pressure. *Nurses' Health Studies* present two cohort investigations performed among younger and older women. One of them demonstrated that in patients who regularly took paracetamol (over 500 mg/24 h), a relative risk (RR) for development of hypertension was considerably higher as compared to women who did not use this drug (RR 1.93 for older women; RR 1.99 for younger) [23]. Moreover, it is worth emphasizing that the risk associated with paracetamol was similar to traditional NSAIDs (RR 1.78 for older women; RR 1.60 for younger). The second cohort investigation carried out in the same study group indicated that in women who frequently used paracetamol (≥ 22 days a month), the risk of serious cardiovascular events (such as heart infarction or cerebral stroke) was nearly the same as after traditional NSAIDs (RR 1.35 for paracetamol; RR 1.44 for traditional NSAIDs). Similarly, application of paracetamol in the amount of 15 tablets or more per week is associated with the risk of cardiovascular events comparable to traditional NSAIDs (RR 1.68 for paracetamol; 1.86 for traditional NSAIDs) [16]. According to the guidelines of the American Heart Association – AHA acetaminophen (paracetamol) is nowadays a drug of choice in patients with concomitant cardiovascular disorders [69]. The prospective double-blind trial was performed in patients with stable coronary disease who used paracetamol at the dose of 1 g three times a day for two weeks and the drug increased their blood pressure. Its effect was similar to that exerted by diclofenac and ibuprofen.

Paracetamol due to its selective action towards COX-2 and similarly to coxibs but contrary to typical NSAIDs does not possess anti-aggregatory properties. The drug does not inhibit blood platelet action when taken at a single oral dose of 1000 mg. However, clinical studies indicate anti-aggregatory action of paracetamol in the case of parenteral administration in high doses [31,49]. Paracetamol can be safely used via the digestive tract: on one hand due to its non-acidic chemical structure (unlike acidic NSAIDs gathering

in the gastric epithelial cells) and on the other hand due to a weak impact on COX-1. However, the results of epidemiological studies suggest that paracetamol at daily doses higher than 2–2.6 g increases the risk of serious side effects in the upper segment of the digestive tract such as bleeding or perforations [60]. Therefore, it is postulated that a long-term effect of paracetamol on the digestive tract should be examined in randomized studies, especially in patients with osteoarthritis who require high doses of this drug for a long time. Paracetamol like coxibs does not induce bronchial spasm in patients with aspirin asthma. In the strategy for treatment of pain in asthmatics, it is recommended to ingest this drug at doses lower than 1000 mg in order to avoid potential bronchial spasm [32].

Bearing in mind a preferential action of paracetamol on COX-2, the differences between the drug discussed and coxibs, selective inhibitors of this isoenzyme, should be emphasised. Paracetamol in opposition to selective inhibitors of COX-2, despite a similar mechanism of action, reveals weak anti-inflammatory activity. It is likely to result from the extracellular accumulation of arachidonic acid and peroxides in the inflammatory tissues, which reduce an inhibitory effect of paracetamol on the prostaglandin production (Fig. 2, p. 5) [9,26]. Indeed, paracetamol did not decrease prostanoid concentrations in the joint fluid of patients suffering from osteoarthritis [64]. On the other hand, paracetamol reduced tissue swelling with similar to ibuprofen efficiency after the oral cavity surgery in humans [8]. There have been also some studies which demonstrated anti-inflammatory action of paracetamol, e.g. nociceptive inhibition and carrageenan-induced rat paw edema [35]. Therefore, at least a weak anti-inflammatory potential of paracetamol cannot be definitely excluded, and further studies are necessary to elucidate the problem.

As regards safety of paracetamol application in pregnancy, prospective cohort studies in humans have not shown an increase in the prevalence of developmental fetal anomalies in pregnant women who took paracetamol in therapeutic doses, although in some experimental studies on animals paracetamol administered at doses twice as high as the maximum single dose demonstrated embryotoxic action [61]. Considering the fact that paracetamol is the drug of choice

in pregnant women, it should be emphasized that epidemiological studies report the possibility of the association between application of this drug in pregnancy and development of asthma in early childhood. The metabolism of paracetamol has been suggested to be responsible for this effect because a large amount of glutathione is used to deactivate the toxic metabolite. Lungs of the developing fetus might deplete glutathione, the main antioxidant of this organ, which can lead to oxidative stress and inflammation of the respiratory airways. In some investigations, the occurrence of wheezing breath in very small children was observed, which, however, is a very weak indicator of asthma [62]. Epidemiological studies from different research centres provide controversial results on the association between paracetamol ingestion by pregnant women and the development of bronchial asthma later in childhood [39,62]. This happens because a number of other factors such as fever, cold, inflammation of fetal membranes or other infections of pregnant women can induce development of asthma in small children, leading thus to falsification of study results. Thus, a randomized study with placebo as a control could solve this problem. However, such a study would be unethical from the point of view of good clinical practice (GCP) which requires application of a standard drug as a comparator, and, as NSAIDs are contraindicated in pregnancy, one group of women with pain and fever would not be treated at all. At present, there is no convincing evidence allowing to unequivocally determine that application of paracetamol in pregnant women may lead to asthma development in small children. Therefore, paracetamol still remains an analgesic and antipyretic drug of choice in pregnant patients. However, it should be stressed that the aforementioned data do not concern complex preparations containing paracetamol or those for i.v. infusion (safety for this route of administration has not been determined due to lack of sufficient clinical data).

Precautions and attempts to counteract toxicity of paracetamol

Due to an easy overdose of paracetamol, the US FDA has proposed to implement new solutions, which to a certain degree would limit this growing problem. A decrease in the maximum permissible single dose of paracetamol from 1000 mg to

650 mg seems to be one of the crucial points. Yet a question arises what will happen to numerous OTC preparations containing paracetamol in the dose exceeding 650 mg (e.g. Choligrip, Febrisan, Gripex Hotactive, Theraflu, Vegantalgin H). It has been suggested that higher doses of this drug, i.e. above 325 mg, should be available only by prescription (according to the information of the US FDA; www.fda.gov). Another suggested solution postulated by FDA is the withdrawal of packages containing high amounts of paracetamol from the market, e.g. containers comprising even 100 single doses (e.g. Apap – 100 tablets, Codipar – 50 tablets, etc.), and the introduction of blisters that should enable the patient to control the amount of ingested drug.

Furthermore, the packaging should be labelled with the information about the risk of liver damage caused by the overuse of the drug. It also seems justifiable to use only one international name, either paracetamol or acetaminophen, and not two different names of the same drug, because it can be misleading for the patient (if not properly informed the unaware patient can ingest the same active substance under different names). The most drastic proposal suggested by FDA is the withdrawal all complex drugs, both available over the counter (OTC) and by prescription, because, as the various study results indicate, they are responsible, to a great degree, for acute paracetamol poisoning. The data obtained by the Toxic Exposure Surveillance System (TESS) in 2005 showed that among all acute paracetamol poisonings, 6.3% (i.e. 3,845 of the 61,289 reported) was caused by OTC preparations and 1.5% (41 of the 2,698 reported) involved severe hepatic damage, while 54% of overdoses (i.e. 1,470 of the 2,698 reported) were recorded in the case of using complex drugs available by prescription. As regards the latter drugs, it has not been completely elucidated to which extent a narcotic ingredient present in the preparation contributed to the poisoning [43]. At present in all complex preparations available by prescription in the USA, a single dose of contained paracetamol cannot exceed 325 mg, whereas the way of the drug dosage, despite a decrease in a single dose, remains the same. Although paracetamol is not so toxic for children as for adults (children do not have a well-developed cytochrome P450 system so the toxic metabolite is not formed), FDA also recommends that liquid paracetamol should be

available only in a single established dose, e.g. 160 mg/5 ml (according to FDA information; www.fda.gov).

Another solution aimed at prevention of paracetamol hepatotoxicity in Great Britain was the introduction of tablets containing paracetamol and methionine, which after the conversion into cysteine and then glutathione in hepatocytes would inactivate the active metabolite, NAPQI. Moreover, due to such a combination there is no time wasted from the moment of intentional or unintentional ingestion of a toxic dose of paracetamol to the application of antidote, e.g. N-acetylcysteine (hepatic damage occurs 24 h after the overdose). Nowadays the only such preparation registered in Great Britain is Paradote (Penn Pharmaceuticals) containing 500 mg of paracetamol and 100 mg of methionine. Other preparations of this type, e.g. Pameton (SmithKline Beecham), have been withdrawn. In other European countries and the USA such combinations of paracetamol do not exist on the pharmaceutical market because so far no efficient and safe dosage of methionine has been established for patients; also safety of the long-term application of these preparations has not been investigated yet (some carcinogenic effect of methionine has been suggested). Besides, the price of such a drug is higher than for a preparation containing paracetamol alone [29].

In the light of novel studies, the application of traditional NSAIDs in combination with paracetamol has not been recommended, particularly when active substances occur in higher doses [30, 60]. Rahme *et al.* (2008) published the retrospective cohort study performed in 644,183 patients aged over 65 years who had been receiving paracetamol (at daily doses: <3 g and >3 g) and/or traditional NSAIDs (with or without a proton pump inhibitor) for 6 years. The risk of hospitalisation due to gastrointestinal events (ulceration, perforation, bleeding from the upper or lower segment of the digestive tract) appeared to be two-fold higher in the case of taking paracetamol in combination with traditional NSAIDs as compared to NSAIDs used in monotherapy. The authors of that study [60] as well as other researchers analysing the problem of interaction between paracetamol and NSAIDs [30] explain the results in relation to the additional COX-1 inhibition caused by paracetamol.

This hypothesis seems to be reliable in the light of new data showing that paracetamol synergistically enhances inhibitory effect of diclofenac on platelet activity [13,49]. Thus, safety and usefulness of complex preparations containing paracetamol combined with NSAIDs appearing on the pharmaceutical market are still the matter of discussion. It is worth paying attention to preparations containing paracetamol and NSAIDs (ibuprofen and propyphenazone) available practically everywhere; on the Polish market such preparations (Cefalgin and Saridon – paracetamol+propyphenazone, and Metafen and Nurofen ultima – paracetamol+ibuprofen) are without a prescription. The aforementioned drugs contain paracetamol at doses of 250 – 500 mg and NSAIDs: ibuprofen – 200 mg or propyphenazone – 150 mg. According to the manufacturers information, a single dose of these drugs is 1-2 tablets with the possibility of three-fold application per day. Considering the maximum dosage (2 tablets 3 times a day), a total dose of paracetamol would range from 1.5 g to 3 g, which is in compliance with the contemporary knowledge [30,60] if used sporadically. It should be remembered that a single dose of paracetamol should not exceed 1 g and daily dose 4 g; the US FDA suggests these values should be decreased to 0.65 g and 3.25 g, respectively. In the case of combined application of paracetamol with NSAIDs, paracetamol dosage should be considerably lower than the aforementioned values.

Conclusions

Paracetamol monotherapy is efficient, well tolerated by the majority of patients and safe, on condition that the drug is administered at therapeutic doses. Table 1 sums up the advantages and disadvantages of paracetamol. We should, however, bear in mind that the paracetamol overuse or application even at therapeutic doses in some situations like improper slimming, smoking, alcohol abuse or ingestion of other medicines, may cause severe hepatic damage or death. Therefore, the question arises as to whether the patient knows that a safe dose of paracetamol (assuming that the above-mentioned situations are not present) comprises only eight tablets à 500 mg or four sachets, each one containing 1000 mg, per day, and that paracetamol is “hidden” in plethora of preparations occurring under different names. Thus,

it is very important to the patient to be warned by doctors or pharmacists about the risk connected with the ingestion and particularly with the overuse of this drug. In the light of new data it appears that despite frequent application of paracetamol as an efficient analgesic and antipyretic drug, the action of this medicament has not been completely understood and this little unknown part may cause irreversible damage to the organism when the drug is overused. A long-term application of high doses of paracetamol carries the risk of adverse reactions typical for COX-2 inhibitors (coxibs) such as hypertension, heart infarction or renal failure. It results from a peripheral selective inhibition of COX-2 by paracetamol. Moreover, it appears that the use of paracetamol combined with NSAIDs is not beneficial because an increase in the occurrence of gastrointestinal events can be observed. On the other hand, i.v. administered paracetamol at high doses inhibits platelet aggregation, which is very important in the treatment of patients with disorders of hemostasis.

It should be remembered that, despite the fact that paracetamol has an unprecedented popularity throughout the world and wide clinical applications, it is not a drug devoid of side effects. Therefore, before taking a decision about the treatment of the patient with paracetamol, each time a balance of benefits and losses should be made so as to perform the adequate and efficient therapy. The aim of the present study is not to deny the rationale of paracetamol use but only to draw the attention of doctors prescribing this drug, and pharmacists selling the drug, as well patients taking it, to the fact that this drug should be used only in situations which are indispensable. Curiously, in the light of its “medical” popularity for decades, an intensive research on its mechanism/s of action in the past and nowadays, and more frequent incidents of its toxicity, it is not possible to answer the question whether we know all about paracetamol, but the nearest years will obviously provide the answer whether the decision taken in 1956 to introduce paracetamol as an OCT drug was correct.

References:

- Alloui A., Chassaing C., Schmidt J., Ardid D., Dubray C., Cloarec A., Eschalier A.: Paracetamol exerts a spinal, tropisetron-reversible, antinociceptive effect in an inflammatory pain model in rats. *Eur J Pharmacol.* 2002; 443(1-3): 71–7.
- Anderson B.J.: Paracetamol (Acetaminophen): mechanisms of action. *Pediatric Anesthesia.* 2008; 18(10): 915–21.
- Aronoff D.M., Oates J.A., Boutaud O.: New insights into the mechanism of action of acetaminophen: its clinical pharmacologic characteristics reflect its inhibition of the two prostaglandin H₂ synthases. *Clin Pharmacol Ther.* 2006; 79(1): 9–19.
- Autret E., Reboul-Marty J., Henry-Launois B., Laborde C., Courcier S., Goehrs J.M., Languillat G., Launois R.: Evaluation of ibuprofen versus aspirin and paracetamol on efficacy and comfort in children with fever. *Eur J Clin Pharmacol.* 1997; 51(5): 367–71.
- Ayoub S.S., Colville-Nash P.R., Willoughby D.A., Botting R.M.: The involvement of a cyclooxygenase 1 gene-derived protein in the antinociceptive action of paracetamol in mice. *Eur J Pharmacol.* 2006; 538(1-3): 57–65.
- Bertolini A., Ferrari A., Ottani A., Guerzoni S., Tacchi R., Leone S.: Paracetamol: new vistas of an old drug. *CNS Drug Rev.* 2006; 12(3-4): 250–75.
- Bjorkman R.: Central antinociceptive effects of non-steroidal anti-inflammatory drugs and paracetamol. Experimental studies in the rat. *Acta Anaesthesiol Scand.* 1995; Suppl 103: 1–44.
- Björnsson G.A., Haanaes H.R., Skoglund L.A.: A randomized, double-blind crossover trial of paracetamol 1000 mg four times daily vs ibuprofen 600 mg: effect on swelling and other postoperative events after third molar surgery. *Br J Clin Pharmacol.* 2003; 55(4): 405–12.
- Boutaud O., Aronoff D.M., Richardson J.H., Marnett L.J., Oates J.A.: Determinants of the cellular specificity of acetaminophen as an inhibitor of prostaglandin H₂ synthases. *Proc Natl Acad Sci USA.* 2002; 99(10): 7130–5.
- Botting R.M.: Inhibitors of cyclooxygenases: mechanisms, selectivity and uses. *J Physiol Pharmacol.* 2006; 57(5): 113–24.
- Botting R.M.: Vane's discovery of the mechanism of action of aspirin changed our understanding of its clinical pharmacology. *Pharmacol Rep.* 2010; 62(3): 518–25.
- Brodie B.B., Axelrod J.: The fate of acetanilide in man. *J Pharmacol Exp Ther.* 1948; 94(1): 29–38.
- Brune K., Hinz B.: Paracetamol, ibuprofen, or a combination of both drugs against knee pain: an excellent new randomised clinical trial answers old questions and suggests new therapeutic recommendations. *Ann Rheum Dis.* 2011; 70(9): 1521–2.
- Bujalska M.: Effect of nitric oxide synthase inhibition on antinociceptive action of different doses of acetaminophen. *Pol J Pharmacol.* 2004; 56(5): 605–10.
- Chan A., Hepp P.: Das Antifebrin, ein neues Fiebermittel. *Centralbl Klein Med.* 1886; 7: 561–4.

16. Chan A.T., Manson J.E., Albert C.M., Chae C.U., Rexrode K.M., Curhan G.C., Rimm E.B., Willett W.C., Fuchs C.S.: Nonsteroidal antiinflammatory drugs, acetaminophen, and the risk of cardiovascular events. *Circulation*. 2006; 113(12): 1578–87.
17. Chandrasekharan N.V., Dai H., Roos K.L., Evanson N.K., Tomsik J., Elton T.S., Simmons D.L.: COX-3, a cyclooxygenase-1 variant inhibited by acetaminophen and other analgesic/antipyretic drugs: cloning, structure, and expression. *Proc Natl Acad Sci USA*. 2002; 99(21): 13926–31.
18. Cannon C.P., Curtis S.P., FitzGerald G.A., Krum H., Kaur A., Bolognese A., Reicin A.S., Bombardier C., Weinblatt M.E., van der Heijde D., Erdmann E., Laine L., MEDAL Steering Committee: Cardiovascular outcomes with etoricoxib and diclofenac in patients with osteoarthritis and rheumatoid arthritis in the multinational etoricoxib and diclofenac arthritis long-term (MEDAL) programme: a randomized comparison. *Lancet*. 2006; 368(9549): 1771–81.
19. Davidson D.G., Eastham W.N.: Acute liver necrosis following overdose of paracetamol. *Br Med J*. 1966; 2(5512): 497–9.
20. Dinchuk J.E., Liu R.Q., Trzaskos J.M.: COX-3: in the wrong frame in mind. *Immunol Lett*. 2003; 86(1): 121.
21. Ferreira S.H., Moncada S., Vane J.R.: Indomethacin and aspirin abolish prostaglandin release from the spleen. *Nat New Biol*. 1971; 231(25): 237–9.
22. Flower R.J., Vane J.R.: Inhibition of prostaglandin synthetase in brain explains the anti-pyretic activity of paracetamol (4-acetamidophenol). *Nature*. 1972; 240(5381): 410–1.
23. Forman J.P., Stampfer M.J., Curhan G.C.: Non-narcotic analgesic dose and risk of incident hypertension in US women. *Hypertension*. 2005; 46(3): 500–7.
24. Fu J.Y., Masferrer J.L., Seibert K., Raz A., Needleman P.: The induction and suppression of prostaglandin H2 synthase (cyclooxygenase) in human monocytes. *J Biol Chem*. 1990; 265(28): 16737–40.
25. Graham G.G., Scott K.F.: Mechanism of action of paracetamol and related analgesics. *Inflammopharmacology*. 2003; 11(4): 401–13.
26. Graham G.G., Scott K.F.: Mechanism of action of paracetamol. *Am J Ther*. 2005; 12(1): 46–55.
27. Graham G.G., Scott K.F., Day R.O.: Tolerability of paracetamol. *Drug Safety*. 2005; 28(3): 227–40.
28. Green K., Drvota V., Vesterqvist O.: Pronounced reduction of in vivo prostacyclin synthesis in humans by acetaminophen (paracetamol). *Prostaglandins*. 1989; 37(3): 311–5.
29. Heptonstall J.P.: Time to make paracetamol with methionine available. *Br Med J*. 2006; 332(7544): 795.
30. Hinz B., Brune K.: Cyclooxygenase-2 – 10 years later. *J Pharmacol Exp Ther*. 2002; 300(2): 367–75.
31. Hinz B., Brune K.: Can drug removals involving cyclooxygenase-2 inhibitors be avoided? A plea for human pharmacology. *Trends Pharmacol Sci*. 2008; 29(8): 391–7.
32. Hinz B., Brune K.: Paracetamol and cyclooxygenase inhibition: is there a cause for concern? *Ann Rheum Dis*. 2012; 71(1): 20–25.
33. Hinz B., Cheremina O., Brune K.: Acetaminophen (paracetamol) is a selective cyclooxygenase-2 inhibitor in man. *FASEB J*. 2008; 22(2): 383–90.
34. Hinz B., Dormann H., Brune K.: More pronounced inhibition of cyclooxygenase 2, increase in blood pressure, and reduction of heart rate by treatment with diclofenac compared with celecoxib and rofecoxib. *Arthritis Rheum*. 2006; 54(1): 282–91.
35. Honoré P., Buritova J., Besson J.M.: Aspirin and acetaminophen reduced both Fos expression in rat lumbar spinal cord and inflammatory signs produced by carrageenan inflammation. *Pain*. 1995; 63(3): 365–75.
36. Howard S.S.: Potential analgesic mechanisms of acetaminophen. *Pain Physician*. 2009; 12(1): 269–80.
37. Högestätt E.D., Jönsson B.A.G., Ermund A.: Conversion of acetaminophen to the bioactive N-acylphenolamine AM404 via fatty acid amide hydrolase-dependent arachidonic acid conjugation in the nervous system. *J Biol Chem*. 2005; 280(36): 31405–12.
38. Ji P., Wang Y., Li Z., Doddapaneni S., Hertz S., Furness S., Sahajwalla C.G.: Regulatory review of acetaminophen clinical pharmacology in young pediatric patients. *J Pharm Sci*. 2012; 101(12): 4383–9.
39. Kang E.M., Lundsberg L.S., Illuzzi J.L., Bracken M.B.: Prenatal exposure to acetaminophen and asthma in children. *Obstet Gynecol*. 2009; 114(6): 1295–306.
40. Kelley B.G., Thayer S.A.: Anandamide transport inhibitor AM404 and structurally related compounds inhibit synaptic transmission between rat hippocampal neurons in culture independent of cannabinoid CB1 receptors. *Eur J Pharmacol*. 2004; 496(1-3): 33–9.
41. Kis B., Snipes J.A., Busija D.W.: Acetaminophen and the cyclooxygenase-3 puzzle: sorting out facts, fictions, and uncertainties. *J Pharmacol Exp Ther*. 2005; 315(1): 1–7.
42. Lanz R., Polster P., Brune K.: Antipyretic analgesics inhibit prostaglandin release from astrocytes and macrophages similarly. *Eur J Pharmacol*. 1986; 130(1-2): 105–9.
43. Larson A.M., Polson J., Fontana R.J., Davern T.J., Lalani E., Hynan L.S., Reisch J.S., Schiødt F.V., Ostapowicz G., Shakil A.O., Lee W.M., Acute Liver Failure Study Group: Acetaminophen-induced acute liver failure: results of a United States multicenter, prospective study. *Hepatology*. 2005; 42(6): 1364–72.
44. Leung L.: From ladder to platform: a new concept for pain management. *J Prim Health Care*. 2012; 4(3): 254–8.
45. Mahadevan S.B., McKiernan P.J., Davies P., Kelly D.A.: Paracetamol induced hepatotoxicity. *Arch Dis Child*. 2006; 91(7): 598–603.
46. Moller P.L., Sindet-Pedersen S., Petersen C.T., Juhl G.I., Dillenschneider A., Skoglund L.A.: Onset of acetaminophen analgesia: comparison of oral and intravenous routes after third molar surgery. *Br J Anaesth*. 2005; 94(5): 642–8.
47. Morse H.N.: Ueber eine neue Darstellungsmethode der Acetylaminodiphenole. *Ber Deutscher Chem Ges*. 1878; 11: 232–3.

48. Mour G., Feinfeld D.A., Caraccio T., McGuigan M.: Acute renal dysfunction in acetaminophen poisoning. *Ren Fail.* 2005; 27(4): 381–3.
49. Munsterhjelm E., Munsterhjelm N.M., Niemi T.T., Ylikorkala O., Neuvonen P.J., Rosenberg P.H.: Dose-dependent inhibition of platelet function by acetaminophen in healthy volunteers. *Anesthesiology.* 2005; 103(4): 712–7.
50. Nakamura K., Li Y.Q., Kaneko T., Katoh H., Negishi M.: Prostaglandin EP3 receptor protein in serotonin and catecholamine cell groups: a double immunofluorescence study in the rat brain. *Neuroscience.* 2001; 103(3): 763–75.
51. Nowak J.Z.: Non-steroidal anti-inflammatory drugs (NSAIDs) in ophthalmology: pharmacological and clinical characteristics. *Mil Pharm Med.* 2012; 5(4): 33–50.
52. Nowak J.Z., Dzielska-Olczak M.: [New NSAIDs and modern formulas/combinations of anti-inflammatory drugs]. *Puls Medycyny.* 2012; educational issue (in Polish).
53. O'Brien W.F., Krammer J., O'Leary T.D., Mastrogiannis D.S.: The effect of acetaminophen on prostacyclin production in pregnant women. *Am J Obstet Gynecol.* 1993; 168(4): 1164–9.
54. Ottani A., Leone S., Sandrini M., Ferrari A., Bertolini A.: The analgesic activity of paracetamol is prevented by the blockade of cannabinoid CB1 receptors. *Eur J Pharmacol.* 2006; 531(1-3): 280–1.
55. Ouellet M., Percival M.D.: Mechanism of acetaminophen inhibition of cyclooxygenase isoforms. *Arch Biochem Biophys.* 2001; 387(2): 273–80.
56. Ovadia H., Wohlman A., Mechoulam R., Weidenfeld J.: Characterization of the hypothermic effect of the synthetic cannabinoid HU-210 in the rat. Relation to the adrenergic system and endogenous pyrogens. *Neuropharmacology.* 1995; 34(2): 175–180.
57. Pasero C., Stannard D.: The role of intravenous acetaminophen in acute pain management: a case-illustrated review. *Pain Management Nursing.* 2012; 13(2): 107–24.
58. Pickering G., Estève V., Lorient M.A., Eschalié A., Dubray C.: Acetaminophen reinforces descending inhibitory pain pathways. *Clin Pharmacol Ther.* 2008; 84(1): 47–51.
59. Pickering G., Lorient M.A., Libert F., Eschalié A., Beaune P., Dubray C.: Analgesic effect of acetaminophen in humans: first evidence of a central serotonergic mechanism. *Clin Pharmacol Ther.* 2006; 79(4): 371–8.
60. Rahme E., Barkun A., Nedjar H., Gaugris S., Watson D.: Hospitalizations for upper and lower GI events associated with traditional NSAIDs and acetaminophen among the elderly in Quebec, Canada. *Am J Gastroenterol.* 2008; 103(4): 872–82.
61. Scialli A.R., Ang R., Breitmeyer J., Royal M.A.: A review of the literature on the effects of acetaminophen on pregnancy outcome. *Reprod Toxicol.* 2010; 30(4): 495–507.
62. Scialli A.R., Ang R., Breitmeyer J., Royal M.A.: Childhood asthma and use during pregnancy of acetaminophen. A critical review. *Reprod Toxicol.* 2010; 30(4): 508–19.
63. Schwab J.M., Beiter T., Linder J.U., Laufer S., Schulz J.E., Meyermann R., Schluesener H.J.: COX-3-a virtual pain target in humans? *FASEB J.* 2003; 17(15): 2174–5.
64. Seppälä E., Nissilä M., Isomäki H., Nuotio P., Nykänen E., Laitinen O., Vapaatalo H.: Comparison of the effects of different anti-inflammatory drugs on synovial fluid prostanoid concentrations in patients with rheumatoid arthritis. *Clin Rheumatol.* 1985; 4(3): 315–20.
65. Simmons D.L., Chandrasekharan N.V., Hu D., Roos K.L., Tomsik J.: Comments on "acetaminophen and the cyclooxygenase-3 puzzle: sorting out facts, fictions, and uncertainties". *J Pharmacol Exp Ther.* 2005; 315(3): 1412–4.
66. Smith H.S.: Potential analgesic mechanisms of acetaminophen. *Pain Physician.* 2009; 12(1): 269–80.
67. Smith J.B., Willis A.L.: Aspirin selectively inhibits prostaglandin production in human platelets. *Nat New Biol.* 1971; 231(25): 235–7.
68. Stirnimann G., Kessebohm K., Lauterburg B.: Liver injury caused by drugs: an update. *Swiss Med Wkly.* 2010; 140: w13080.
69. Sudano I., Flammer A.J., Roas S., Enseleit F., Noll G., Ruschitzka F.: Nonsteroidal anti-inflammatory drugs, acetaminophen, and hypertension. *Curr Hypertens Rep.* 2012; 14(4): 304–9.
70. Swierkosz T.A., Jordan L., McBride M., McGough K., Devlin J., Botting R.M.: Actions of paracetamol on cyclooxygenases in tissue and cell homogenates of mouse and rabbit. *Med Sci Monit.* 2002; 8(12): BR496–503.
71. Walson P.D., Jones J., Chesney R., Rodarte A.: Antipyretic efficacy and tolerability of a single intravenous dose of the acetaminophen prodrug propacetamol in children: a randomized, double-blind, placebo-controlled trial. *Clin Ther.* 2006; 28(5): 762–9.
72. Waring W.S.: Criteria for acetylcysteine treatment and clinical outcomes after paracetamol poisoning. *Expert Rev Clin Pharmacol.* 2012; 5(3): 311–8.
73. Warner T.D., Vojnovic I., Giuliano F., Jiménez R., Bishop-Bailey D., Mitchell J.A.: Cyclooxygenases 1, 2, and 3 and the production of prostaglandin I2: investigating the activities of acetaminophen and cyclooxygenase-2-selective inhibitors in rat tissues. *J Pharmacol Exp Ther.* 2004; 310(2): 642–7.
74. Vane J.R.: Inhibition of prostaglandin synthesis as a mechanism of action for aspirin-like drugs. *Nat New Biol.* 1971; 231(25): 232–5.
75. Von Mering J.: Beitrage zur Kenntniss der Antipyretica. *Ther Monatsch.* 1893; 7: 577–87.
76. Xie W.L., Chipman J.G., Robertson D.L., Erikson R.L., Simmons D.L.: Expression of a mitogen-responsive gene encoding prostaglandin synthase is regulated by mRNA splicing. *Proc Natl Acad Sci USA.* 1991; 88(7): 2692–6.
77. Zygmunt P.M., Chuang H., Movahed P., Julius D., Högestätt E.D.: The anandamide transport inhibitor AM404 activates vanilloid receptors. *Eur J Pharmacol.* 2000; 396(1): 39–42.

