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ACETYSALICYLIC ACID (ASA) AND NON-STEROIDAL ANTI-INFLAMMATORY DRUGS (NSAID) FOR PREVENTION OF THROMBOSIS AND CANCER

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Summary

A trend towards a reduced risk of thrombosis and cancer has been observed among people taking acetylsalicylic acid (ASA) or any of nonsteroidal anti-inflammatory drugs (NSAID). ASA is the active substance in both German Aspirin and Croatian Andol. The key action of these drugs is that they block cyclooxygenase (COX) enzymes catalyzing the conversion of arachidonic acid (ADA) to prostaglandins (PG) and thromboxanes (TXA). ADA metabolites are associated with inflammatory process, thrombosis, carcinogenesis and tumor growth. Increased expression of COX-2 has been observed in both inflammations and tumors including: head and neck tumors, tumors of the upper aerodigestive tract, oropharyngeal leukoplakia, premalignant oral lesions, pancreatic, esophageal, gastric and skin cancer, melanoma, prostate, urinary bladder, lung, ovarian and cervical cancer, lymphoma, leukemia, breast cancer, colon cancer, etc. ASA and NSAID act preventively at the COX level and reduce the occurrence and growth of tumors, enhancing the radio- and chemotherapy effect on tumor. Besides at the COX level, ASA/NSAID also show antitumor activity at other levels acting as inhibitors of: aromatase gene, transforming growth factor-β (TGF-β), platelet-derived growth factor (PDGF), insulin-like growth factor (IGF), activator protein-1 (AP-1), serine kinase IKK-β, nuclear factor kappa B (NF-κB), urokinase-type plasminogen activator (μPA), mitogen-activated protein p38 (p38 MAP) activation, etc. In addition, ASA/NSAIDs are efficient in other diseases including: infections, rheumatism, diabetes mellitus, blood vessel diseases, hypertension, eclampsia, Alzheimer's disease, etc. To reduce the occurrence of cancer, the World Health Organisation promotes decreased body mass, increased physical activity and plant-based diet, which contains fewer calories, abounds in cellulose fibers, vitamins and ASA. Exceeding the recommended dose of ASA may cause serious side effects. On the other hand, 5-aminosalicylic acid (5-ASA), shown to successfully treat gastrointestinal inflammations (GIT) and reduce risk of tumor occurrence causes less adverse side effects. Nitric oxide-donating aspirin (NO-ASA) and nitric oxide-donating NSAID (NO-NSAID) do not cause damage to the gastrointestinal mucosa, and they are very successful in the treatment of inflammation and prevention of intestinal and other cancers. Under medical supervision, low doses of ASA / NSAID are recommended to be taken daily for cancer prevention, then after cancer surgery and during chemotherapy and radiotherapy to reduce the risk of cancer recurrence and thrombosis.

KEY WORDS: *acetylsalicylic acid (ASA), nonsteroidal anti-inflammatory drugs (NSAID), 5-aminosalicylic acid (5-ASA), nitric oxide-donating aspirin (NO-ASA), nitric oxide-donating NSAID (NO-NSAID), cyclooxygenase (COX), arachidonic acid (ADA), prostaglandins (PG), thromboxanes (TXA), cancer, thrombosis*

ACETILSALICILNA KISELINA (ASA) I NESTEROIDNI PROTUUPALNI LIJEKOVI (NSAID) U PREVENCIJI TROMBOZE I RAKA

Sažetak

Uočen je smanjen rizik pojave tromboze i raka u ljudi koji su rabili acetilsalicilnu kiselinu (ASA) ili neke druge lijekove iz skupine nesteroidnih protuupalnih lijekova (NSAID). ASA je aktivni sastojak njemačkog Aspirina i hrvatskog Andola. Ključ djelovanja tih lijekova je blokada enzima ciklooksigenaze (COX) koji sudjeluju u razgradnji arahidonske kiseline (ADA) na prostaglandine (PG) i tromboksane (TXA). Metaboliti ADA povezani su s upalom, trombozom, karci-

nogenezom i rastom tumora. Pojačana ekspresija COX-2 uočena je u upalama i tumorima kao što su: tumori glave i vrata, gornjeg aerodigestivnog trakta, orofaringelane leukoplakije, premaligne oralne lezije, karcinom pankreasa, ezofagusa, želuca, raka kože, melanoma, prostate, mjehura, pluća, jajnika, vrata maternice, limfoma, leukemije, dojke, crijeva, itd. ASA i NSAID djeluju preventivno na razini COX-a i smanjuju pojavu i rast tumora, te pojačavaju učinak zračenja i kemoterapije na tumor. Osim na razini COX-a, ASA/NSAID djeluju antitumorski i na drugim razinama, kao što su inhibicije: aromatase gena, transformirajućeg faktora rasta β (TGF-β), faktora rasta iz trombocita (PDGF), insulinu sličnog faktora rasta (IGF), aktivatora proteina-1 (AP-1), serine kinaza IKK-β, nuklearni faktor kappa B (NF-κB), urokinazni aktivator plasminogena (μPA), aktivacija mitogenom aktiviranog proteina p38 (p38 MAP), itd. Koristan je učinak ASA/NSAID i u drugim bolestima kao što su: infekcije, reuma, diabetes mellitus, krvožilne bolesti, hipertenzija, eklampsija, Alzheimerova bolest, itd. Radi smanjenja pojavnosti karcinoma Svjetska zdravstvena organizacija propagira manju tjelesnu masu, veću fizičku aktivnost i biljnu prehranu koja je manje kalorična, bogata celuloznim vlaknima, vitaminima i ASA. Zbog neželjenih nuspojava, prekoračenje dozvoljenih doza ASA može biti opasno. Manje neželjenih posljedica ima 5-aminosalicilna kiselina (5-ASA) koja uspješno liječi upale probavnog trakta (GIT) i smanjuje rizik pojave tumora. NO-ASA i NSAID (NO-NSAID), ne oštećuju sluznicu probavnog trakta. Vrlo su uspješni u liječenju upale i prevenciji raka crijeva i ostalih rakova.

Uz liječničku kontrolu ASA / NSAID se preporučaju svakodnevno u malim dozama za prevenciju raka, te poslije operacije raka, u tijeku liječenja raka kemoterapijom i radioterapijom za smanjenje rizika recidiva i tromboze.

KLJUČNE RIJEČI: *acetilsalicilna kiselina (ASA), nesteroidni protuupalni lijekovi anti- (NSAID), 5-aminosalicilna kiselina (5-ASA), NO-ASA, NO-NSAID, ciklooksigenaza (COX), arahidonska kiselina (ADA), prostaglandini (PG), tromboksani(TXA), rak, tromboza*

INTRODUCTION

On the scale of all diseases, cancer is steadily climbing the top. Cancer treatment is very expensive. New drug therapies are constantly being searched, and their studies and development largely funded compared to the prevention which is much less represented. From the distant past already, willow bark, now known to contain ASA as its active compound, has been a folk remedy for aches, fever and rheumatism. Studies have shown that ASA and other NSAIDs play an important role in the prevention of thrombosis and cancer. ASA / NSAID are cheap and readily available drugs which, in the future, may take on the key role in the prevention of the above diseases.

ASA

ASA is one of the most widely used medicines and the first synthesized drug in the world. Felix Hoffman, a German chemist synthesized the drug for the Bayer Company in 1897. In essentially the same form, the drug has been used for more than a century as analgesic, antipyretic, anti-inflammatory and anti-aggregation agent. It has shown to be useful in the prevention and prophylaxis of cardiac, blood vessel and malignant diseases, and Alzheimer's. For centuries, traditional medicine uses the bark of the willow tree (Latin name: Salix alba), a natural form of aspirin, as a remedy for fever, inflammation, pain and rheumatism.

ASA and non-selective NSAIDs primarily act as inhibitors of COX-1 and COX-2 enzymes, unlike selective NSAIDs that block only COX-2 (Figure 1). ASA irreversibly inhibits COX-1 by acetylating serine 530 taking the highest position at the hydrophobic channel of COX-1 and preventing access of arachidonic acid to its action site. COX inhibition reduces the production of PG and TXA. For explaining the mechanism of

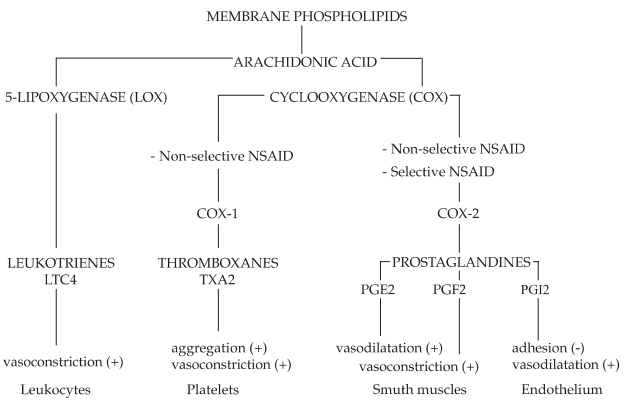

Figure 1. The primary effect of ASA / NSAID on the metabolism of arachidonic acid.

action for ASA, Sir John Robert Vane was awarded the 1982 Nobel Prize in physiology and medicine (1, 2).

The irreversible inhibition is important in platelets that have no nucleus and thus no new gene expression for new COX formation. Therefore, the inhibition continues throughout the platelet life-span – which is about a week. During this, platelets do not aggregate and the risk of developing undesirable clots is therefore reduced.

For its acidic properties, liver metabolites of its own degradation and interrupted PGI_2 synthesis, ASA can cause damage to the gastric mucosa. The reduced synthesis of PGI_2 reduces the formation of bicarbonates and mucus, resulting in a reduced protection of the gastric mucosa.

COX-1, COX-1, COX-3

In human cells, isoforms of the following COX enzymes are found: COX-1, COX-2 (3, 4), and COX-3 (5). COX-3 is a splice variant of COX-1 especially sensitive to acetaminophen. It acts as a mediator of both pain and fever. Acetaminophen has little effect on COX-1 and COX-2, so it does not produce any anti-inflammatory effect (5).

COX-1 was first isolated in 1976 (6). COX-2 and COX-3 were discovered in 1992 (7) and 2002 (5), respectively. The COX enzymes are situated at the endoplasmic reticulum and at the nuclear membrane. They are a product of various genes found as follows: COX-1 on chromosome 9q32-q33.3, COX-2 on chromosome 1q25.2-q25.3 (8,9). In simple species, COX-1 and COX-2 are 60% identical. COX-1 is a glycoprotein with 576 amino acids of the molecular mass of 70 kDa (10). COX-2 has 604 amino acids and the molecular mass of 70 kDa (11).

COX-1 is mostly found in the gastrointestinal tract, kidneys, vascular smooth muscles and platelets. COX-2 can be found in the brain tissue, kidneys, megakaryocytes and newly formed platelets. In other normal tissues, COX-2 is not detectible. The expression may be quickly induced by various stimulants such as: cytokines, growth factor, oncogenes and tumor promoters. It is detectible in many tumors. There is no so strict distinction between COX-1 and COX-2, as COX-1 may also be induced by similar agents (12,13). Individuals carrying heterozygous COX-1 haplotype A-842G/C50T are more sensitive to ASA (14).

The inflammatory stimulants, including lipopolysaccharides and pro-inflammatory cytokines (interleukin IL-1β, tumor necrosis factor (TNF), growth factors, demonstrate 10-20-fold enhancement of COX-2 expression in nuclei containing cells. Corticosteroids and interleukins IL-4, IL-10 and IL-13 inhibit the expression of COX-2 (15).

ADA AND COX

COX enzymes mediate the decomposition of ADA into TXA_2 and PG. A portion of ADA is decomposed by the 5-liopoxygenase (5-LOX) enzymes into leukotrienes that induce bronchospasm in asthma. PGs have many physiologic effects. PGs act mostly though G protein coupled receptors (GPCR), although they can also act through the peroxisome proliferator-activated receptor (PPAR).

PGs formed through action of COX-1 under normal physiologic conditions are local, paracrine hormones important for the production of mucus, bicarbonates, platelet aggregation and production, vasoconstriction, cell growth, water excretion, pressure regulation, erection and parturition. PGs formed under pathophysiologic conditions, where the activity of COX-2 is increased, play a role in the inflammatory process, fever, pain, cellular transformation, tumor growth and metastasizing. Synthetic PGs are administered to accelerate parturition or abortion, in the treatment and prevention of peptic ulcus, in Reynaud's phenomenon, ischemia, pulmonary hypertension, in the treatment of heart defects (foramen ovale), glaucoma and erectile dysfunction. COX-1 inhibition results in gastrointestinal bleeding and toxic effects affecting kidneys, while the inhibition of COX-2 produces analgesic, antipyretic, anti-inflammatory and anti-cancer effects. In the inflammatory response, PGE_2 is the principal COX product. It induces dilatation of vascular smooth muscles manifested by skin redness. Vasodilatation increases edema, while bradykinin and histamine augment the vascular permeability (16). COX-1, present in the normal stomach, mediates the production of PGs respon-

sible for the increased production of mucosa, bicarbonates, inhibition of acid secretion, increased blood flow in the abdominal wall, accelerated migration and adherence of granulocytes to endothelium. This self-protective mechanism is held responsible for the normal gastric mucosa. The blockade of COX-1 interrupts this mechanism, potentially causing damage to the gastric mucosa and resulting in ulceration (17,18). Therefore, more selective COX inhibitors, both demonstrating the anti-inflammatory activity and preserving the gastric mucosa, have been sought (coxib drugs).

PGE_2 activates an inflammatory response, produces pain and raises the body temperature, and gets stimulated by interleukin-1 (IL-1) during bacterial and viral infections. It plays a role in the reproductive processes. It induces parturition by provoking the uterine contractions. In the kidneys, it regulates proliferation of keratinocytes. PGs increase blood flow through the kidney. In addition, they take part in calcium traffic, hormone regulation and cell growth. TXA_2 stimulates platelet aggregation and vasoconstriction, which play a role in clot formation, stoppage of bleeding and increased heart workload.

POSITIVE EFFECT OF ASA / NSAID

A lower incidence of cancer has been reported in people taking aspirin or other NSAIDs. These drugs inhibit COX and reduce the synthesis of PG. PGs stimulate aromatase gene expression and thus promote the synthesis of estrogens. Aromatase converts adrenal androgens to estrogens that can induce breast cancer. The blockade of COX-2 may be useful in the prevention of estrogen-positive breast tumors. Daily intake of ASA is inversely associated with the risk of breast cancer development (19,20).

ASA reduces the neutrophil activation by platelets, inhibits the synthesis of PGI_2 in endothelial cells of blood vessels, increasing endothelial production of nitric oxide (eNOS) and reducing the inflammatory response (21,22). ASA provides protection atherosclerosis by preventing oxidation of low density lipoproteins (LDL) (23,24). Fibrinogen becomes oxidized and converts to fibrin, an inflammatory component that increases the risk of thrombosis. The antioxidant effect of ASA on fibrinogen reduces the risk of thrombosis development (25). ASA acetylates plasma proteins including fibrinogen and thus accelerates its decomposition – fibrinolysis (26-28). In this combination of effects, ASA reduces the inflammation and thrombosis, as well as the risk of blood vessel occlusion (29).

ASA inhibits the proliferation of cells by transforming growth factor-β (TGF-β) that blocks cell-cycle progression at G_0 phase, by blocking the platelet-derived growth factor (PDGF) and insulin-like growth factor (IGF). The relationship between ASA and TGF-β can explain effects on cancer chemoprevention, immunomodulation and wound healing (30). ASA can inhibit the phospholipase activity that plays a role in the intracellular signal transfer (31).

ASA / NSAIDs act protective against skin cancer by inhibiting the activator protein-1(AP-1) induced by ultraviolet B (UVB) rays (32-35). UV radiation increases the skin levels of PGE_2, this potent regulator of keratinocyte proliferation. ASA blocks PG (36). High doses of ASA induce COX inhibition-independent apoptosis, and inhibit serine kinase IKKβ thereby improving glucose tolerance in patients with Type 2 diabetes (37). ASA also induces tumor cell apoptosis. It results in cytochrome C release from mitochondria, which interacts with the apoptotic protease activating factor (APAF-1). Caspase proteases become activated resulting in tumor cell death (38,39). Tumor cell apoptosis results from ASA inhibition of nuclear factor kappa B (NF-κB) (40), and activation of the p38 mitogen-activated protein (p38 MAP) kinase (41). NF-κB is involved in the expression of various cellular genes playing a role in the regulation of the inflammatory response. ASA is helpful in the therapy of polycythemia vera (42). ASA inhibits ornithine decarboxylase by reducing the growth of tumor (43). Plasma iron acts as a free radical that induces the formation of other free radicals. ASA stimulates ferritin expression and thus decreased the free radical level (44). In perioxidase decomposition of ADA, free radicals are also released, which may be involved in mutagenesis and tumor promotion. ASA blocks the decomposition of ADA and thus reduces the number of dangerous free radicals (Table 1).

Table 1.

TARGETS AND BENEFICIAL EFFECTS OF ASA / NSAID

ASA / NSAID Targets	ASA / NSAID Positive effects	References
⇓ COX-1, COX-2	⇓ thromboxanes ⇓ prostaglandins ⇓ aggregation ⇓ thrombosis ⇑ vasodilatation ⇓ fever ⇓ inflammation ⇓ pain ⇓ cancer	1, 2
⇓ expression aromatase gene	⇓ estrogen ⇓ cancer	19, 20
⇓ platelet-neutrophil interactions	⇓ inflammation ⇓ thrombosis	21,22,29
⇑ endothelial nitrogen oxide synthesis (eNOS)	⇓ inflammation	21,22
⇓ low density lipoproteins (LDL) oxidation	⇓ thrombosis ⇓ atherosclerosis	23,24
⇓ fibrinogen oxidation	⇓ thrombosis	25
⇑ fibrinogen acetylation	⇑ fibrinolysis ⇓ thrombosis	26-28
⇓ transforming growth factor -β TGF-β	⇓ cancer	30
⇓ platelet-derived growth factor (PDGF)	⇓ cancer	30
⇓ insulin-like growth factor (IGF)	⇓ cancer	30
⇓ phospholipase - intracellular signaling transduction	⇓ cancer	31
⇓ activator protein-1 (AP-1) induced by ultraviolet-B	⇓ skin cancer ⇓ melanoma	32-35
High dose - ⇑ COX independent apoptosis	⇓ cancer	37
⇓ serine kinase IKK-?	⇓ glucose ⇓ cancer ⇓ aggregation ⇓ thrombosis	37,116,118
⇑ cytochrome C release - interaction with apoptotic protease activating factor (APAF-1)- ⇑ activation caspase proteases	⇑ apoptosis ⇓ cancer	38,39
nuclear factor kappa B (NF- κB) urokinase-type plasminogen activator (μPA)	⇓ inflammation ⇑ apoptosis ⇓ cancer	40,60
⇑ p38 mitogen-activated protein (p38 MAP) kinase	⇑ apoptosis ⇓ cancer	41
⇓ polycythemia vera	⇓ polycythemia vera	42
⇓ ornithine decarboxylase	⇑ apoptosis ⇓ cancer	43
⇑ ferritin synthesis	⇓ free radicals ⇓ mutagenesis ⇓ cancer	44

CANCER AND INCREASED COX-2 EXPRESSION

The increased expression of COX-2 has been observed in pancreatic cancer. The use of COX-2 inhibitors induces apoptosis in cells with increased COX-2 expression (45). ASA has shown good results in the prevention of esophageal cancer since it induces apoptosis of tumor cells (46). Patients with gastric cancer and increased COX-2 expression have a worse prognosis (47). COX-2 expression plays an important role in the pathogenesis of skin cancer including melanoma (48-51). In addition, increased expression of COX-2, dependent upon progression of cancer, has also been shown in prostate cancer. Selective COX-2 inhibitors induce apoptosis, suppress angiogenesis and reduce the growth of prostate

tumor cells (52-59). The increased concentration of urokinase-type plasminogen activator (μPA) in the plasma indicates a poorer cancer prognosis. ASA / NSAIDs inhibit nuclear factor kappa B (NF-κB) which results in μPA suppression, and thus in reduced adhesion and migration of prostate cancer cells (60). In cancer of the urinary bladder, COX-2 positively correlates with disease worsening and its blockade is a potential target for chemoprevention of this type of tumor (61-63). Non-small cell lung cancer (NSCLC) regresses with COX-2 inhibition. The administration of ASA / NSAIDs is associated with a 61-68% reduced risk of developing lung cancer (64-72). In ovarian cancer, in which COX-1 expression is also increased, NSAIDs have shown effective in stopping tumor growth (73, 74). Cervical carcinoma also shows increased expression of COX-1 having a positive correlation with cancer neoangiogenes (75). B-cell lymphoma as well shows COX-2 expression whose inhibition may provide a positive treatment effect (76). Individuals taking ASA at least twice a week, show a reduced incidence of leukemia (77). NFκB is associated with tumor growth and found in transformed lymphocyte cell lines (Hodgkin's and Reed-Sternberg' cells). ASA blocks NF-κB and stops the growth of Hodgkin's cells (78).

In breast cancer, COX-2 expression has been reported in 36-79% of the cases (79). A positive correlation between COX-2 expression and angiogenesis has been assessed in breast carcinoma (80). NSAIDs inhibit carcinogenesis of the breast (81). In breast tumors, COX-2 expression is accompanied with an increased production of PGE_2, inducing angiogenesis and progression of the tumor (82). In breast tumor patients with increased expression of COX-2, the time period to disease recurrence is shorter, and there is a positive correlation between hormone-receptor status, HER-2/neu expression, stage of the disease and lymph node status (83,84).

In colorectal tumor, COX-2 is localized to epithelial cells, macrophages, fibroblasts and vascular endothelium. PGs formed by the enzymatic activity of COX-2 react with local malignant epithelial cells by inhibiting apoptosis and enhancing cell migration. The inhibition of PG production may suppress the formation of intestinal polyps or their transformation to cancer. One of the first studies showed a 40% lower risk of developing colon cancer in individuals using ASA compared to those who did not (85). The expression of COX-2 was shown to be increased in 50% of adenoma and 85% of adenocarcinoma of the colon. An increased level of COX-2 and PG was revealed in familial adenomatous polyps (FAP), which may transform to a carcinoma (86). A 50% reduced risk of developing colon cancer was observed in NSAIDs users (87). The use of ASA 16 or more times a month during 6 years reduced the risk of developing carcinoma of the colon and rectum for 42% and 34%, respectively. A ten-year use of ASA reduced the risk of developing cancer for 64% (88). It was noted that regular daily use of 100 mg ASA over a year had a chemopreventive effect in the early stage of colorectal carcinogenesis. Aberrant crypti foci (ACF) were reduced for 64-82% per cm^2 of colorectal mucosa, and ACF dysplasia for 52%. The reduction was greater in the distal portion of the colorectum (89). With the same effect as higher doses, 81 mg ASA daily significantly reduces PGE_2, trophic factor in human rectal mucosa (90-92). In the animal model, ASA inhibits chemically induced intestinal carcinogenesis

Table 2.

THE EFFECT OF ASA / NSAID ON SOME CONDITIONS WITH INCREASED COX-2 EXPRESSION

COX-2 overexpression	
ASA / NSAID effects	References
⇓ Inflammation	15,95
⇓ Diabetes mellitus	37
⇓ Head and neck cancer	103
⇓ Upper aerodigestive tract	99
⇓ Oropharyngeal leukoplakia	101
⇓ Premalignant oral lesions	103
⇓ Pancreatic cancer	45
⇓ Esophageal cancer	46,100
⇓ Gastric cancer	47,100
⇓ Skin cancers & melanoma	48-51
⇓ Prostate cancer	52-59
⇓ Bladder cancer	61-63
⇓ Lung cancer	64-72
⇓ Ovarian cancer	73,74
⇓ Cervical cancer	75
⇓ B-cell lymphoma	76
⇓ Leukemia	77,78
⇓ Hodgkin's	79
⇓ Breast cancer	80-85
⇓ Colorectal cancer	86-99

(93-95). An increase of C-reactive protein (CRP) in plasma has been reported in individuals developing intestinal cancer, thereby supporting the hypothesis that inflammation is a risk factor for developing intestinal carcinoma (96). COX-2 expression in colorectal cells results in an altered behavioral pattern of the surrounding endothelial cells whose COX-1 plays a significant role in the angiogenesis response (97,98). The incidence of mouth, throat and esophageal tumors in ASA users is three-fold lower than in non-users ASA (99,100). COX inhibition is shown to be useful in oral leukoplakia (tobacco-related malignancy) and in the prevention of head and neck tumors (101-103). COX inhibitors are generally considered to be useful in cancer prevention (104).

ASA / NSAID AND RADIOTHERAPY

It is likely that COX inhibition enhances the effect of radiotherapy by acting both directly on the tumor and indirectly on the tumor vasculature (105,106). The suppression of PG progression enhances *in vitro* tumor cell radiosensitivity (107). Few hours after irradiation, PG, TXA_2 and TXB_2 levels are raised and remain raised for a week. The increased levels of PG and its synthetic analogues (misoprostol, iloprost) protect cells against radiation. If administered before irradiation, they act as radioprotectors both *in vitro* and *in vivo* (108-111).

ASA / NSAID AND CHEMOTHERAPY

The administration of COX inhibitors enhances also the effect of chemotherapy. The introduction of NSAID in the chemotherapy protocol for gastric cancer results in a significant life prolongation of the patients (112). In chemoresistant ovarian carcinoma, increased expression of COX-2 and poorer patient survival has been observed (113). Chemotherapy induces the expression of COX-2 in NSCLC (114).

ASA / NSAID AND OTHER DISEASES

In patients with diabetes mellitus, increased production of TXA_2, increased platelet aggregability and increased risk for developing thrombosis have been reported. Compared to healthy individuals, patients with diabetes are more prone to inflammations that usually last longer, for inflammation promotes cell resistance to insulin. Inflammation and insulin resistance may be associated with the development of intestinal cancer (115). In diabetes mellitus, vascular COX-2 expression and vasoconstriction are increased. As ASA and NSAIDs block COX-2 expression, vasodilatation occurs and the kidney is more efficient (116). In diabetes mellitus, ASA reduces inflammation, lowers blood sugar levels, enhances cell sensitivity to insulin and reduces the risk of myocardial infarction and thrombosis (117). Body mass index (BMI), physical activity and nutrition are associated with the insulin level and insulin-like growth factor (IGF), which may play a role in the development of cancer (118-120).

An increased TXA_2 level, and thereby a tendency toward thrombosis, has been observed in eclampsia and hypertension in pregnant women. Low-doses of ASA have demonstrated a protective effect on the occurrence of eclampsia (121). ASA protects endothelial cells and has a beneficial effect in atherosclerosis (122-123). ASA reduces virulence of staphylococcus aureusa (124). ASA and NSAIDs may reduce the risk of developing Alzheimer's disease (125).

5-ASA, NO-ASA, NO-NSAID

With the aim of making good use of the positive effect and avoiding unwanted side effects of ASA and NSAIDs, 5-aminosalicylic acid (5-ASA) has been synthesized to successfully treat inflammation of the gastrointestinal tract (GIT) (126). Nitric oxide (NO) has been shown to stimulate vasodilatation and enhance secretion of mucus that protects the gastrointestinal tract. NO can neutralize adverse effects ASA and NSAIDs exert on GIT mucosa. For this reason, nitric oxide-donating aspirin (NO-ASA) and NO-NSAID have been synthesized. These drugs have shown to be very successful in the chemoprevention of intestinal cancer and other cancers, too (127-129).

ASA / NSAID, NUTRITION AND CANCER

It has been observed that vegetarians are less likely to develop colorectal cancer. Individ-

Table 3.
POTENTIAL CONSEQUENCES OF ASA / NSAID OVERDOSE

ASA / NSAID overdose			
1.	Tinnitus	8.	Hypotension
2.	Abdominal pain	9.	Hallucination
3.	Hypokaliemia	10.	Renal failure
4.	Hypoglycemia	11.	Confusion
5.	Pyrexia	12.	Seizure
6.	Hyperventilation	13.	Coma
7.	Dysrhytmia	14.	Death

uals taking low-dose ASA have a serum ASA level similar to vegetarians, as ASA is a natural compound common in many plants (130). The World Health Organisation stresses the importance of nutrition and lifestyle in cancer prevention. Eating fruits and vegetables provides health benefits, as well as enhanced physical activity, lean body mass and reduced nicotine and alcohol intake (131). However, ASA overdose may produce unwanted effects (Table 3).

CONCLUSION

ASA / NSAIDs reduce the risk of developing cancer and thrombosis. These drugs, which are cheap and available over the counter, have a very beneficial effect. Individuals who are not oversensitive to ASA / NSAIDs, who do not have any gastrointestinal disorders, are not prone to bleeding, and do not have any hematological disease, may occasionally, or on alternate days, take low-dose ASA for prevention. These drugs might be useful after tumor surgery and in cancer chemotherapy and radiotherapy for preventing tumor recurrence and the development of thrombosis. Although easily available, ASA/NSAIDs should not be used without a consultation with a doctor.

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