INFLUENCE OF ACETYLSALICYLIC ACID ON HEMATOTOXICITY OF BENZENE

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Abstract

Objectives: The aim of the study was to evaluate the influence of acetylsalicylic acid (ASA) on benzene hematotoxicity in rats. Materials and Methods: The study was carried out on rats exposed for 2, 4 and 8 weeks to benzene vapour at a concentration of 1.5 or 4.5 mmol/m³ of air (5 days per week, 6 hours per day) alone or together with ASA at the doses of 5, 150 or 300 mg/kg body weight (per os). Results: Benzene at a concentration of 4.5 mmol/m³ caused a slight lymphopenia, granulocytosis and reticulocytosis in blood. In bone marrow traits of megaloblastic renewal, presence of undifferentiated cells and giant forms of granulocytes as well as an increase in myeloperoxidase and decrease in chloroacetate esterase activity and lipids content were noted. ASA (150 and 300 mg/kg b.w.) influenced some of hematological parameters, altered by benzene intoxication. ASA limited the solvent-induced alteration in blood reticulocyte count and in the case of bone marrow in the erythroblasts count. Traits of megaloblastic renewal in bone marrow were less pronounced. Besides, higher activity of myeloperoxidase and the decrease in the level of lipids in granulocytes were noted. Conclusion: Our results suggest that ASA limited the benzene-induced hematotoxicity.

Key words:
Benzene, Acetylsalicylic acid, Interactions, Hematotoxicity, Blood, Bone marrow

INTRODUCTION

Occupational exposure to benzene is a frequent cause of chronic toxicity, which may result in induction of aplastic anemia and neoplastic processes, including leukemias, as well as breast and lung tumors. Proliferative disorders of the hemopoietic system, which most frequently develop in humans exposed to benzene, include chronic myeloid leukemia, acute myeloid leukemia, lymphoblastic leukemia, malignant lymphoma and multiple myeloma. Development of tumors of the hemopoietic system reflects the damage to bone marrow pluripotent stem cells, which leads to anemia, leukopenia or thrombocytopenia and, then, to fully symptomatic aplastic anemia or myeloid leukemia [1,2]. The mechanism of benzene hematotoxicity is not clear yet. One theory stresses the importance of active benzene metabolites and cellular DNA adducts, particularly inherited in somatic cell lines, which cause inability of the cells to react to cytokines, resulting in excessive proliferation. Chromosomal aberrations induced by binding active benzene metabolites to DNA may also lead to oncogenes activation or antioncogenes inactivation [3–5].

Another hypothesis is associated with stimulatory functions of the bone marrow microenvironment. Cytotoxic damage of bone marrow stromal cells and macrophages, in particular induced by benzene and its metabolites, affects their capacity to control proliferation and differentiation.
ASA inhibits inflammatory processes by prostaglandin and nitric oxide production, which may result in reduction of hematotoxic effects of benzene [17,22,25].

The aim of our study was to investigate the effect of oral acetylsalicylic acid administration on hematotoxicity of benzene after inhalation exposure.

MATERIALS AND METHODS

Animals

The studies were performed on male Wistar rats. The animals originated from the breeding farm of the Department of Toxicology, Poznan University of Medical Sciences. The body weight of each rat was 230±15 g. The rats were housed in controlled light conditions (12 h light : 12 h dark), at 22°C and relative humidity of 60±10%. The animals were fed with standard laboratory chow with free access to tap water.

Treatment protocols

The animals were subjected to inhalatory exposure to benzene (Sigma-Aldrich) vapour at a concentration of 1.5 mmol/m$^3$ (37 ppm) or 4.5 mmol/m$^3$ (112 ppm). The exposure took place in a dynamic toxicological chamber for 5 days a week, 6 h every day, for a period of 2, 4 or 8 weeks. Concentration of the solvent inside the toxicological chamber was monitored by gas chromatographic analysis of air samples with 30 min intervals (packed column Supelco: 5% DIDP/ 5% Bentone 34 on 80/100 Chromosorb W AW, 6’×1/8” SS, column temperature 80°C, carrier gas flow 20 cm$^3$/min, FID detector, sample volume 10 cm$^3$). Before each exposure, the rats received an aqueous suspension of ASA (Sigma-Aldrich) administered p.o. at a dose of 5 mg/kg b.w. (1/300 DL$_{50}$) or 150 mg/kg b.w. (1/10 DL$_{50}$) or 300 mg/kg b.w. (1/5 DL$_{50}$). On the 3rd day after exposure cycle termination, blood was sampled from the heart of superficially anesthetized rats. In the blood, hemoglobin concentration, hematocrit of stem cells. Failure to synthesize normal signaling polypeptides results in uncontrolled proliferation of cells which would otherwise be inhibited or the cells would be forced to differentiate into individual cell lines. In a similar way, a disturbed immune system including lymphocytes and stromal macrophages may also lead to development of neoplastic cells, which in physiological conditions would be detected and selected out by the immune surveillance mechanisms [6–10].

Hematotoxic activity of benzene involves both, the solvent and its metabolites. Induction of the cytochrome P-450 system, especially CYP 2E1 and CYP 2B1, which participates in metabolic activation of benzene, may lead to intensification of the observed alterations [11–13]. It has been demonstrated that acetylsalicylic acid (ASA), a widely used non-steroid anti-inflammatory drug, induces cytochrome P-450. Therefore, its prolonged administration for the purpose of prevention of cardiac and cerebral infarcts may lead to metabolic interactions with other xenobiotics, including benzene [14–16].

ASA may also modify toxic effects of benzene by inhibition of transcription factor κB, which participates in activation of genes involved in synthesis of inflammatory factors as well as being responsible for proliferation and maturation of T lymphocytes [17,18]. Hydroquinone, a benzene metabolite, exhibits a similar activity – it inhibits transcription and translocation of the κB factor to the cell nucleus by suppression of the translocation pathway composed of protein kinase B (Akt), kinase IkBβ (IKKβ) and inhibitor α of κB protein (IκBα) [10,19,20].

Secondary activation of benzene metabolites in bone marrow to the highly reactive compounds is paralleled by formation of free radicals and is responsible for cell membrane damage and genotoxicity [3,5,21]. ASA-induced inhibition of prostaglandin G2 transformations, resulting from repression of endogenous synthase, may lower activity of macrophage peroxidase and, thus, the capacity to form active metabolites [22–24].