Pharmacological Modulation of Acute Radiation Disease by Meloxicam, an Inhibitor of Cyclooxygenase-2

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Introduction

Current protective and therapeutic approaches to pharmacological modulation of acute radiation syndromes are based on combined modality treatments and deserve supplementations targeted at increasing treatment efficacy and at reducing doses of individual components with accompanying mitigation of undesirable side effects. Earlier studied non-selective cyclooxygenase inhibitors, known as classical non-steroidal anti-inflammatory drugs (NSAIDs), turned out in animal studies to be not only effective stimulators of radiation-suppressed hematopoiesis but also inducers of serious gastrointestinal side effects. Meloxicam, a selective cyclooxygenase-2 inhibitor, retains production of prostaglandins in gastrointestinal tissues and its therapeutic profile in terms of gastrointestinal side effects is much better in comparison with classical NSAIDs. This communication summarizes data from our experiments on the effects of meloxicam in experimental mice in pre-irradiation (protective) and post-irradiation (therapeutic) treatment regimens.

Materials and Methods

Mice: B10CBAF$_1$ mice aged three months were used throughout the experiments.

Irradiation: The mice were whole-body irradiated at a dose rate of 0.15 Gy/min using a γ-ray source (Chisostat, Chirana, Praha, Czech Republic).

Meloxicam (Sigma, St. Louis, MO, USA) was dissolved in sterile saline and administered intraperitoneally in doses of 20 mg/kg. Sterile saline was used for control injections.

Hematological techniques: A complex analysis of hematopoiesis in experimental mice including determination of numbers of cells in compartments of progenitor, precursor, and mature blood cells has been performed. Serum concentrations of granulocyte colony-stimulating factor (G-CSF) have been assessed my the ELISA technique.

Thirty-day survival of the experimental mice was evaluated after lethal radiation exposures.

Statistics: Data are shown as means ± SEM. One-way ANOVA and Tukey *post hoc* test have been used for statistical evaluation of hematopoietic parameters. Differences in thirty-day survival have been assessed by Fisher's exact test.

Results 1

Meloxicam stimulates hematopoiesis when administered in a single dose 1 hour before irradiation with a sublethal dose of 6.5 Gy γ-rays (Tables 1 and 2).

Table 1. Hematological parameters determined on days 5, 10, and 15 after 6.5 Gy of gamma irradiation in mice pretreated one hour before irradiation with a single dose of meloxicam or saline. Part 1 – findings in the bone marrow.

	Irradiated meloxicam-treated mice	Unirradiated untreated controls	Irradiated saline-treated controls	Factor of increase
Total nucleated cells per femur x 10^6		21.229 ± 0.956		
Day 5	1.660 ± 0.086		1.670 ± 0.132	1.00
Day 10	4.126 ± 0.286		3.927 ± 0.277	1.05
Day 15	11.812 ± 1.241		9.044 ± 0.891	1.31
GM-CFC per femur x 10^3		17.983 ± 0.817		
Day 5	0.223 ± 0.045**a**		0.078 ± 0.016	2.86
Day 10	1.149 ± 0.336		0.310 ± 0.119	3.71
Day 15	8.352 ± 1.637		4.184 ± 0.967	2.00
BFU-E per femur x 10^3		23.735 ± 1.580		
Day 5	0.040 ± 0.007**aa**		0.016 ± 0.003	2.50
Day 10	1.646 ± 0.600		1.732 ± 0.586	0.95
Day 15	16.743 ± 2.920		16.089 ± 1.603	1.04

Values are given as means ± SEM. Ten mice per group were used. Each experiment was performed once.
a, aa, P<0.05 and P<0.01, respectively, compared to irradiated saline-treated controls.

Table 2. Hematological parameters determined on days 5, 10, and 15 after 6.5 Gy of gamma- irradiation in mice pretreated one hour before irradiation with a single dose of meloxicam or saline.
Part 2 –findings in the peripheral blood.

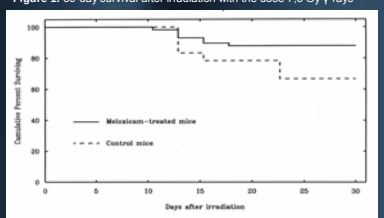
	Irradiated meloxicam-treated mice	Unirradiated untreated controls	Irradiated saline-treated controls	Factor of increase
Neutrophils per μL of blood x 10^3		1.130 ± 0.045		
Day 5	0.287 ± 0.068		0.092 ± 0.033	3.12
Day 10	0.050 ± 0.038		0.000 ± 0.000	N.D.
Day 15	1.327 ± 0.315**a**		0.532 ± 0.153	2.49
Erythrocytes per μL of blood x 10^6		8.093 ± 0.237		
Day 5	6.844 ± 0.107		6.664 ± 0.134	1.03
Day 10	6.012 ± 0.153		5.586 ± 0.223	1.08
Day 15	6.252 ± 0.205**aa**		4.828 ± 0.280	1.29

Values are given as means ± SEM. Ten mice per group were used. Each experiment was performed once. a, aa, P<0.05 and P<0.01, respectively, compared to irradiated saline-treated controls.

Results 2

Meloxicam increases 30-day survival in mice when administered 1 hour before irradiation with a mid-lethal dose of 7.5 Gy γ-rays (Fig. 1).

Figure 1: 30-day survival after irradiation with the dose 7,5 Gy γ-rays



Fourty-eight to 50 mice per group. Survival of meloxicam-treated mice: 85%. Survival of control mice: 64%. Statistical significance: P < 0.01.

Results 3

Meloxicam stimulates hematopoiesis when administered in four daily doses on days 3, 4, 5, and 6 after irradiation with a sublethal dose of 4 Gy γ-rays (Table 3).

Table 3. Hematological parameters on day 7 after irradiation with 4 Gy of gamma-rays in mice treated with meloxicam on days 3, 4, 5, and 6 after irradiation

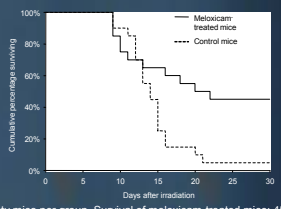
	Irradiated meloxicam-treated mice	Irradiated saline-treated controls	Factor of increase
Total nucleated cells per femur x 10^6	**17.26 ± 3.43**	**15.97 ± 2.09**	**1.08 ± 0.26**
GM-CFC per femur x 10^3	**12.66 ± 1.00^{aa}**	**7.745 ± 0.904**	**1.64 ± 0.23**
Neutrophils per μL of blood x 10^3	**1.594 ± 0.225^{aa}**	**0.860 ± 0.154**	**1.85 ± 0.42**
BFU-E per femur x 10^3	**12.60 ± 1.28^{aa}**	**7.883 ± 0.511**	**1.60 ± 0.19**
Erythrocytes per μL of blood x 10^6	**7.189 ± 0.714**	**7.760 ± 0.390**	**0.93 ± 0.10**

Values are given as means ± SEM. Ten mice per group were used. Each experiment was performed twice.
^{aa}, P<0.01, compared to irradiated saline-treated controls.

Results 4

Meloxicam increases 30-day survival when administered in a single dose in an early postirradiation interval of 1 hour after radiation exposure to a lethal dose of 9 Gy γ-rays (Fig. 2).

Figure 2: 30-day survival after irradiation with the dose of 9 Gy γ-rays



Twenty mice per group. Survival of meloxicam-treated mice: 45% .
Survival of control mice: 5%. Statistical significance: P < 0.01.

Results 5

Meloxicam elevates serum levels of G-CSF when given in various treatment regimens before or after irradiation of mice with sublethal or lethal doses of γ-rays (results not shown).

Conclusions

Meloxicam, a selective cyclooxygenase-2 inhibitor, stimulates hematopoiesis in mice when given in a pre-irradiation (protective) regimen, as well as when administered post-irradiation (therapeutically).

Contrary to the "classical", non-selective NSAIDs, meloxicam increases survival of mice exposed to lethal doses of ionizing radiation. This positive effect of meloxicam is probably caused by much lesser undesirable side effect of this drug on the gastrointestinal system in comparison with the classical NSAIDs.

Important from the practical point of view is the finding that a mere single dose of meloxicam given shortly (1 hour) after irradiation, i.e., in a therapeutic regimen, induces clear positive effect on survival.

The described qualities of meloxicam strongly suggest that the indications for the treatment of patients with meloxicam should be exteded by the indication of myelosuppression of various origin.