Antitumor effects of a cyclooxygenase-2 inhibitor, meloxicam, alone and in combination with radiation and/or 5-fluorouracil in cultured tumor cells

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Abstract. To ascertain whether meloxicam used in a clinical setting as a non-steroidal anti-inflammatory drug (NSAID) warrants preclinical *in vivo* evaluation as an anticancer agent, we investigated its antitumor effects alone and in combination with radiation and/or 5-fluorouracil (5-FU) in cultured cells. Seven cell lines were examined for cyclooxygenase-2 (COX-2) protein expression by immunoblot analysis, and the HeLaS3, SCCVII and EMT6 cell lines were selected, expressing relatively high, intermediate, and relatively low COX-2 levels, respectively. Antitumor effects were examined using a colony assay. Among the three cell lines, the effect of meloxicam alone was strongest in SCCVII cells. With 24 h of drug exposure, meloxicam at concentrations of 250 and 1250 μM had a definite antitumor effect, dependent on the drug exposure time. The effect of meloxicam in combination with radiation and/or 5-FU was also investigated in the SCCVII cells. At a meloxicam concentration of 250 μM, the antitumor effect in combination with radiation or 5-FU was increased compared to the effect of radiation or 5-FU alone; however, the combined effect appeared to be additive. At lower concentrations, meloxicam had no radiosensitizing effect, nor did it enhance the effect of 5-FU. A meloxicam concentration of 250 μM is considerably higher than concentrations obtained in humans taking meloxicam as an NSAID. In conclusion, the antitumor effect of meloxicam was not correlated with the level of COX-2 protein expression. The effect of meloxicam in combination with radiation and/or 5-FU appeared to be additive. To evaluate the possibility of using meloxicam as an anticancer agent, *in vivo* investigations at clinically relevant drug dose levels are required.

Introduction

COX-2, one of the two isoforms of cyclooxygenase (COX), is an inducible enzyme associated with inflammatory disease and cancer (1) that is overexpressed in many malignant tumors, including colorectal, prostate, breast and lung cancers (2-5). Hence, COX-2 may be a therapeutic target in cancer therapy. Selective inhibitors of COX-2 have been reported to reduce the formation, growth and metastasis of experimental tumors. Among the COX-2 inhibitors that show promise in cancer therapy is celecoxib, which shows marked efficacy against experimental tumors (6,7) and is currently the subject of ongoing clinical trials (8,9).

Meloxicam, developed as a non-steroidal anti-inflammatory drug (NSAID), has been shown to have inhibitory actions against COX-2 (10,11) and antitumor effects in several human tumor cell lines (7,12-14). The *in vivo* effects of meloxicam have also been reported, though not in detail (15-17). Since meloxicam has been widely used as an NSAID, its toxicity in humans as well as in animals is well known. Thus, if meloxicam proves to have a potential clinical use in anticancer therapy, toxicity studies may to a large extent be spared. This would be very advantageous for clinical investigators.

However, based on previous investigations of meloxicam, it is unclear whether it may be expected to have an antitumor effect in the clinical setting. Nevertheless, some investigators are already attempting to administer meloxicam as an anticancer agent to cancer patients, despite the lack of sufficient preclinical studies (see UMIN Clinical Trials Registry: https://center.umin.ac.jp/). We are of the opinion that a number of issues should be addressed in laboratory studies prior to the use of meloxicam as an anticancer agent in clinical trials. For example, the dependency of the effect of meloxicam on COX-2 protein expression levels has not been elucidated. If the effect of meloxicam alone is weak, it may be possible to combine the drug with other chemotherapeutic agents and/or radiation therapy. Under certain experimental conditions, meloxicam has been reported to have radiosensitizing properties (18,19).

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However, these combined effects need to be investigated in further detail. We therefore carried out the present *in vitro* investigation of the effect of meloxicam alone and in combination with radiation and/or 5-fluorouracil (5-FU), with the aim of addressing the abovementioned issues prior to performing systematic *in vivo* preclinical studies.

Materials and methods

Cell lines. In order to select cell lines with different levels of COX-2 protein expression, seven tumor cell lines stocked in our laboratories were initially analyzed for COX-2 protein expression. The cell lines examined were KNS42 neuro-epithelial tumor, U87MG and U251MG human malignant glioma, V79 Chinese hamster lung fibroblast, HeLaS3 human cervical cancer, EMT6 mammary sarcoma and SCCVII mouse squamous cell carcinoma. The characteristics of several of these cell lines have been described previously (20,21). The cells were cultured in Eagle's minimum essential medium (MEM) containing 10% (for KNS42, U87MG and U251MG) or 12.5% (for the remaining lines) fetal bovine serum.

Immunoblot analysis. The seven cell lines were harvested using a cell scraper (Sumitomo Bakelite, Tokyo, Japan), and their proteins were extracted with 1% sodium dodecyl sulfate (Wako, Osaka, Japan) per 50 mM Tris-HCl + 150 mM NaCl (pH 7.6) (TBS). Subsequently, 15 μg of the proteins were subjected to electrophoresis on a 10% polyacrylamide gel and transferred to polyvinylidene difluoride membranes (Immobilon-P, Millipore Corp., Billerica, MA, USA). The membranes were then blocked from nonspecific absorption with 5% fat-free milk/TBS. Anti-COX-2 mouse monoclonal antibodies (1:1000; Cayman Chemical, Ann Arbor, MI, USA) and anti-actin mouse monoclonal antibodies (1:20,000; Sigma, St. Louis, MO, USA) were used as the primary antibodies. The secondary antibody was peroxidase-labeled anti-mouse immunoglobulin antibody (1:4000; Dako Japan, Tokyo). Chemical lighting was produced by an Enhanced Chemiluminescence Plus kit (Amersham, Chiltern Hills, UK) and detected by a luminoimage analyzer LAS-1000 (Fuji Film, Tokyo, Japan).

Meloxicam, 5-FU and radiation. The three selected cell lines were treated with meloxicam alone or with radiation and/or 5-FU. 5-FU was chosen as it is one of the most commonly used anticancer agents and is quite often combined with radiation therapy. The concentrations of 5-FU investigated in this study were derived from our previous study, as were the experimental procedures (22). Meloxicam, provided courtesy of Daiichi-Sankyo Pharmaceutical (Tokyo, Japan), was dissolved in dimethylsulfoxide at concentrations 100 times higher than the test concentration and then diluted with the culture medium. 5-FU was purchased from Sigma Aldrich Co. Ltd. (St. Louis, MO, USA) and dissolved in medium at concentrations 10 times higher than the test concentration. Radiation was administered with a 210-kVp X-ray machine (10 mA, 2-mm Al filter, 1.6 Gy/min; Chubu Medical Co. Ltd., Matsusaka, Japan) as previously described (23).

Cytotoxic treatment and colony assay. Cells were subcultured on the day before the experiment to maintain exponential
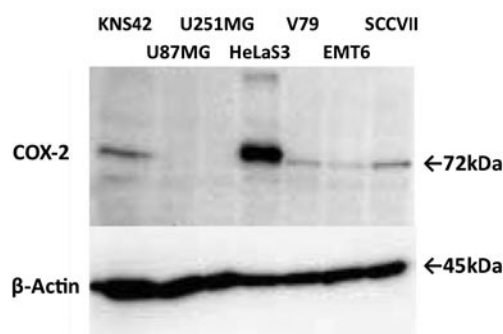

Figure 1. Immunoblot analysis of COX-2 protein expression in seven cell lines. ß-actin was used as a loading control for the immunoblot.
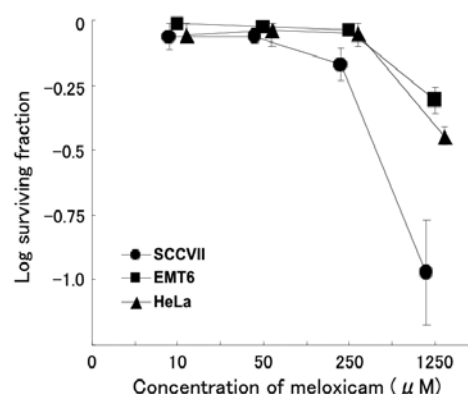.

Figure 2. Survival of three tumor cell lines after treatment for 24 h with various concentrations of meloxicam. Points represent the SE of 4 experiments.

growth. The cells were trypsinized, and the cell number in the suspensions was counted using a Coulter counter. Appropriate numbers of cells were plated onto 5-cm culture dishes. After a minimum of half an hour, MEM containing various concentrations of meloxicam or 5-FU, or MEM containing vehicle only (as a control) was added, or radiation was administered. The medium was removed 6-72 h later and replaced with fresh medium after rinsing with phosphate-buffered saline. Subsequently, the drugs were kept in medium for 168 h until cell fixation and staining. Cells were harvested 168 h after the start of treatment, fixed with 70% ethanol, and stained with Giemsa. Colonies containing ≥50 cells were counted. Differences in the cell surviving fraction between pairs of groups were examined by the paired t-test. A P-value <0.05 was considered to indicate statistical significance.

Results

Fig. 1 shows the results of the immunoblot analysis of COX-2 protein expression in the seven cell lines. HeLaS3 showed the strongest expression, while U87MG, U251MG and EMT6 showed weak or almost no expression. KNS42, V79 and SCCVII showed intermediate levels of COX-2 protein expression. Considering these results and the ease of handling, HeLaS3, SCCVII and EMT6, cell lines expressing strong, moderate and weak levels of COX-2 protein, respectively,
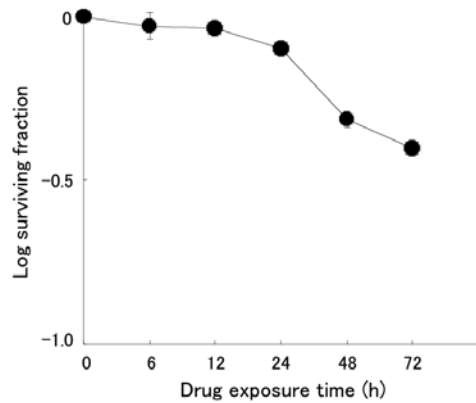
Figure 3. Survival of SCCVII cells after exposure to 250 μM meloxicam for various hours. Points represent the SE of 4 experiments.

Figure 5. Survival of SCCVII cells after exposure to 10 μM 5-FU with or without various concentrations of meloxicam for 24 h. Points represent the SE of 4 experiments.
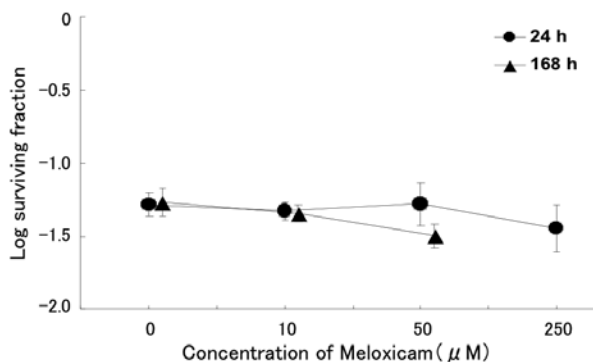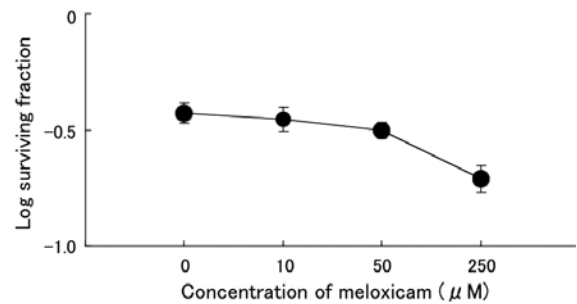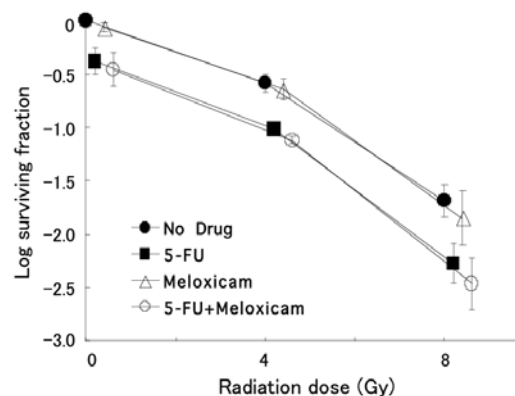

Figure 4. Survival of SCCVII cells after irradiation at 6 Gy with or without exposure to various concentrations of meloxicam for 24 or 168 h. Points represent the SE of 4 experiments.

Figure 6. Survival of SCCVII cells as a function of radiation dose with or without a 24-h exposure to 5 μM 5-FU and/or 150 μM meloxicam. Points represent the SE of 4 experiments.

were selected for the next experiment examining the efficacy of meloxicam.

Fig. 2 shows the survival of the three cell lines after a 24-h exposure to various concentrations of meloxicam alone. At a concentration of 250 μM, meloxicam had a significant cytotoxic effect on just the SCCVII cells. At 1250 μM, it had cytotoxicity in all three lines. The effect of meloxicam was stronger in SCCVII cells than in EMT6 cells (P=0.012). Thus, meloxicam was considered to be most effective in the SCCVII cells with moderate COX-2 protein expression, and SCCVII cells were used for subsequent experiments.

Fig. 3 shows the effect of 250 μM meloxicam on SCCVII cells as a function of drug exposure time, between 6 and 72 h. The effect of meloxicam was drug exposure time-dependent, and was significant at exposure times of $\geq$12 h. The effect was especially strong at durations of 48 or 72 h.

Fig. 4 shows the effect of various concentrations of meloxicam added to medium for 24 or 168 h in combination with radiation at 6 Gy on SCCVII cells. After 24 h of drug exposure, meloxicam at a concentration of $\leq$50 μM had no cytotoxicity (data not shown) and no radiosensitizing effect. At 250 μM, as shown in Fig. 2, meloxicam had cytotoxicity. Radiation plus 250 μM meloxicam was more efficient than radiation alone (P=0.035). The mean log surviving fraction

(SF) $\pm$ SD for the combination (-1.45$\pm$0.33) was equal to the sum of the log SF $\pm$ SD of meloxicam alone (-0.17$\pm$0.19) and that of radiation alone (-1.28$\pm$0.16), suggesting that this combined effect was additive. After 168 h of drug exposure, meloxicam had no cytotoxicity at 10 μM (log SF = -0.0059$\pm$0.010) and exhibited no radiosensitizing effect. At 50 μM, it also had no cytotoxicity (log SF = -0.0061$\pm$0.010), nor was radiation plus meloxicam at this concentration significantly more efficient than radiation alone (log SF = -1.54$\pm$0.12 vs. -1.31$\pm$0.16, P=0.15). At 250 μM, meloxicam killed all the cells.

Fig. 5 shows the combined effect of meloxicam and 5-FU. After 24 h of drug exposure, the effect of 10 or 50 μM of meloxicam (having no cytotoxicity alone) in combination with 10 μM of 5-FU was similar to that of 5-FU alone. At 250 μM, meloxicam plus 5-FU (10 μM) was more effective than 5-FU alone, with a mean log SF ($\pm$SD) of -0.71$\pm$0.11; not significantly lower than the sum of that of meloxicam alone (-0.17$\pm$0.19) or 5-FU alone (-0.43$\pm$0.09). Consequently, the effect could not be regarded as synergistic. When 2.5 μM of 5-FU was administered to SCCVII cells for 168 h with or without meloxicam, no cells survived.

Finally, the combined effect of meloxicam, 5-FU and radiation was investigated. Based on the preceding results, concentrations of meloxicam and 5-FU of 150 and 5 μM,

respectively, were selected, and radiation doses of 4 and 8 Gy were applied. The cells were treated with the drugs for 24 h. Fig. 6 shows that, with a radiation dose of 0 Gy, 150 μM of meloxicam alone had no effect and 5 μM of 5-FU alone had a modest effect. At radiation doses of 4 and 8 Gy, the combined effect of meloxicam, 5-FU and radiation were similar to the effect of 5-FU plus radiation.

Discussion

Initially, the antitumor effects of COX-2 inhibitors were considered to emanate from COX-2 inhibition. It was therefore postulated that their antitumor efficacy is dependant on the level of COX-2 protein expression in tumors (14,24,25). However, in the present study, meloxicam activity was not clearly correlated with the degree of COX-2 protein expression. The antitumor activity of another COX-2 inhibitor, celecoxib (which has been much more vigorously investigated as an antitumor agent than meloxicam), has been reported to be partially independent of COX-2 inhibition (7,26,27). There are a few studies reporting a similar observation with meloxicam, with which our results agree (14,19). On the one hand, there is clear evidence that COX-2 is an important player in the expression of antitumor effects. On the other hand, an increasing number of reports indicate that COX-2 inhibitors do not require the presence of COX-2 to exert their antitumor activities. Our results and those of previous studies indicate that the correlation between COX-2 expression and the antitumor activity of COX-2 inhibitors is moderate or limited. The COX-2-independent antitumor effects of selective COX-2 inhibitors have recently been discussed in detail (28,29).

Several COX-2 inhibitors have been investigated for their radiosensitizing and chemosensitizing activities, as COX-2 inhibition leads to the decreased production of prostaglandins, which are involved in tumor resistance to radiation and chemotherapy (18,19,30,31). In the present study, the combined effect of meloxicam and radiation or 5-FU was observed. The effects of the combination of meloxicam with radiation and of meloxicam with 5-FU were considered to be additive. In a study by Bijnsdorp *et al* (18) using three human glioma cell lines, meloxicam at a concentration of 750 μM with a drug exposure time of 24 h was found to have a radiosensitizing effect (synergistic effect with radiation) in two of the lines, whereas no such effect was had in the third. This concentration of meloxicam had significant growth suppressive effects, but no cytotoxic effects. In this study, meloxicam was not observed to have a radiosensitizing effect. It is unclear whether the discrepancy between the results of the study by Bijnsdorp *et al* (18) and the present study is due solely to the difference in cell lines used. *In vivo*, the suppression of angiogenesis may be expected as a result of COX-2 inhibition, possibly leading to the potentiation of antitumor effects. However, due to the lack of universally observed radiosensitizing or chemosensitizing effects *in vitro*, it might be optimistic to expect meloxicam to have a definitive effect as a radiosensitizer or chemosensitizer *in vivo* and in humans.

The cytotoxic effect of meloxicam alone was observed at concentrations of 250 μM or higher with a drug-exposure time of 24 h in SCCVII cells, which were the most sensitive to meloxicam of the three cell lines tested. With a drug exposure time of 168 h, a concentration greater than 50 μM appeared to be required for meloxicam to exhibit definite antitumor effects. In a previous study, meloxicam was shown to have cytotoxicity at a concentration of 5 μM with an exposure time of 14 days (12). In the clinic, up to 15 mg of meloxicam is used for pain relief; after the administration of this dose, the peak concentration of meloxicam is reported to be approximately 3 μg/ml (equal to 8.5 μM) (http://www.drugs.com/pro/meloxicam. html). A limited number of studies have indicated the *in vivo* efficacy of meloxicam against experimental tumors. In one study, a meloxicam dose of 1.0 to 5.0 mg/kg administered daily was shown to be effective, and the drug concentration following a 1.0 mg/kg dose appeared to be achievable in humans (32). However, in another study the effective daily dose of meloxicam was 40 mg/kg. This dose is apparently higher than the doses of meloxicam administered to humans as an NSAID (12). Consequently, further *in vivo* studies are necessary to investigate the antitumor effect of meloxicam at clinically relevant drug dose levels before it is used as an antitumor drug. With the currently available data, we suspect that the effect of meloxicam, if it has any influence, may not be significant at the doses applied for pain killing purposes. Attempts at escalating the dose of meloxicam would therefore appear to be necessary for an antitumor effect to be expected in human patients.

In conclusion, the antitumor effect of meloxicam was not observed to be correlated with COX-2 protein expression levels, and the effect of meloxicam in combination with radiation and/or 5-FU appeared to be additive. To evaluate the possibility of using meloxicam as an anticancer agent, *in vivo* investigations at clinically relevant drug dose levels are required.

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