Transactions on Materials, Biotechnology and Life Sciences
ISSN: 2960-1932, eISSN: 2960-2319 | Volume 7
MISBP 2024

Metabolic kinetics and safety assessment of the antitumor drug meloxicam

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Abstract. Meloxicam is a selective cyclooxygenase-2 (COX-2) inhibitor with anti-inflammatory effects, and its anti-tumour effects have been the subject of considerable attention in recent years. This research provides a comprehensive analysis of the studies on the anti-tumour aspects of meloxicam, including the mechanism of anti-tumour action, basic pharmacokinetic studies, and an evaluation of the safety profile. The anti-tumour mechanism of meloxicam is primarily characterized by the inhibition of the COX-2/PGE2 signaling pathway, the regulation of apoptosis-related proteins, the inhibition of tumour angiogenesis and the regulation of immune function. In terms of pharmacokinetics, meloxicam has rapid oral absorption, high bioavailability and wide distribution. It is mainly metabolized by the liver, undergoing hydroxylation and oxidation to form biologically inactive metabolites. With an elimination half-life of approximately 20 hours, the safety evaluation is primarily concerned with the assessment of potential gastrointestinal, hepatic, renal and cardiovascular adverse reactions that may arise from long-term use. The application of nanotechnology has the potential to mitigate the observed toxicity).

Keywords: Meloxicam; Antineoplastic drug; Pharmacokinetics; Safety evaluation.

1. Introduction

Meloxicam has been extensively documented for its efficacious anti-inflammatory effects as a selective cyclooxygenase-2 (COX-2) inhibitor [1, 2]. The anti-tumour properties of meloxicam have emerged as a prominent area of interest, attracting significant attention. As research into tumour treatment progresses, it is vital to conduct relevant safety evaluations and metabolic kinetic studies on meloxicam. This not only facilitates a more comprehensive understanding of the mechanism of action and potential risks of meloxicam in oncology treatment, but also provides a scientific basis for its rational application in oncology treatment. Meloxicam exerts its anti-tumour effects through a range of intricate and nuanced mechanisms. One of the principal mechanisms is the inhibition of the COX-2/PGE2 signalling pathway. The effective inhibition of this signalling pathway can block important pathways for the growth and spread of tumour cells, thus providing strong support for anti-tumour therapy. Meloxicam can regulate apoptosis-related proteins, prompting tumour cells to move towards apoptosis and thereby curbing the development of tumours fundamentally. Its inhibitory effect on tumour angiogenesis should not be underestimated, as this limits tumour growth and metastasis by reducing the blood supply to tumours.

Despite meloxicam's demonstrated efficacy in anti-tumour therapy, it is imperative to acknowledge the numerous unresolved questions pertaining to its metabolic profile and safety profile. The administration of the drug may result in the potential toxicity of vital organs, such as the liver and kidneys. As the primary metabolic and excretory organs of the human body, the liver and kidney play a pivotal role in the processing of drugs. The accumulation of the drug within the body can subsequently lead to damage to vital organs such as the liver and kidneys. This potential risk is particularly acute in patients with pre-existing liver and kidney disease. Consideration must be given to the application of this treatment in special populations. The elderly, children, pregnant women and individuals with other underlying medical conditions exhibit distinct physiological characteristics and metabolic processes compared to the general population, and their tolerance to and metabolism of the drug may also differ. A comprehensive grasp of meloxicam's metabolic dynamics, encompassing

absorption, distribution, metabolism, and excretion, is indispensable for the refinement of the dosing regimen. By gaining insight into the dynamic process of the drug within the body, a personalised dosing regimen can be formulated for each patient, ensuring that the drug achieves its intended therapeutic effect while minimising the risk of adverse reactions. An understanding of the distribution characteristics of drugs can facilitate the targeting of different types of tumours for precise treatment and improve the efficacy of drugs. The objective of this research is to present a comprehensive overview of the anti-tumour pharmacokinetics and safety profile of meloxicam, based on the latest research findings on its anti-tumour properties. By conducting a comprehensive analysis of meloxicam's mechanism of action, metabolic kinetics, and safety profile, this research offers valuable insights and guidance for its optimal utilisation in tumour therapy.

2. Anti-tumour mechanism

The action mechanism of meloxicam in the field of anti-tumour research has emerged as a prominent area of investigation, driven by the continuous deepening of research on tumours. At present, research on the anti-tumour mechanism of meloxicam is primarily concentrated on the following pivotal areas.

Meloxicam has been demonstrated to exert significant anti-tumour effects by inhibiting the COX-2/PGE2 signalling pathway. During the development of tumours, the expression of COX-2 is frequently elevated in tumour cells. This overexpression markedly accelerates tumour development and deterioration, while also creating an environment conducive to tumour cell growth, proliferation, invasion and metastasis. Meloxicam selectively inhibits the activity of COX-2, a key action that reduces the production of prostaglandin E2 (PGE2), which plays an important role in tumour progression. The inhibition of PGE2 by meloxicam effectively suppresses tumour cell proliferation, invasion and metastasis. Meloxicam could markedly diminish the migratory and invasive capabilities of breast cancer cells, thereby exerting a pronounced inhibitory effect on tumour progression [1], providing a significant theoretical foundation for the potential use of meloxicam in the treatment of breast cancer.

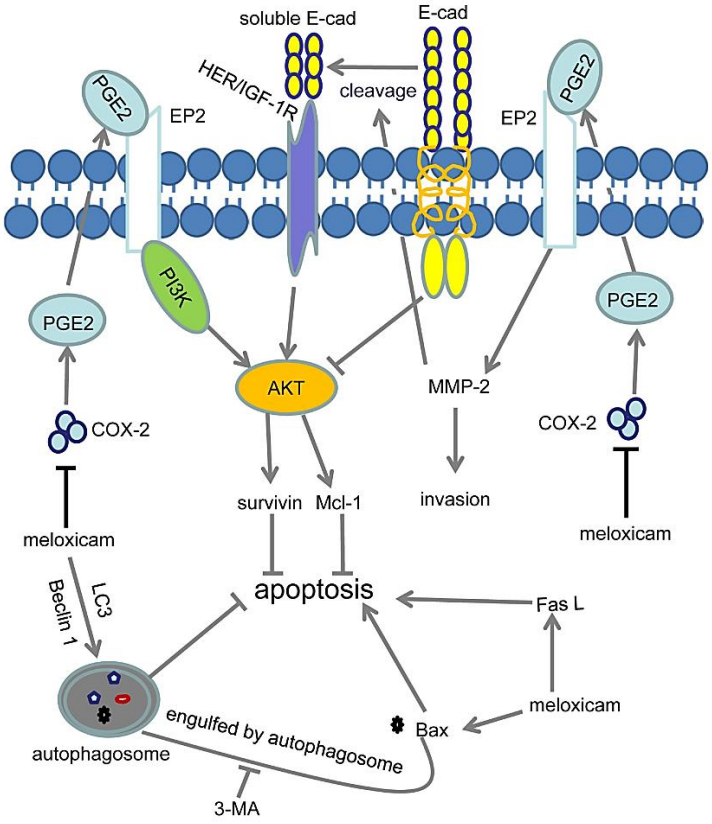

Figure 1. Proposed mechanism of anti-tumour effect [2].

Meloxicam plays a pivotal role in regulating the expression of proteins involved in apoptosis, and it can up-regulate the expression of pro-apoptotic proteins and down-regulate the expression of anti-apoptotic proteins. The regulatory mechanism in question enables meloxicam to effectively promote the apoptosis of tumour cells. Apoptosis represents a fundamental physiological process, indispensable for the maintenance of normal organismal function. In tumour cells, the apoptotic mechanism is frequently suppressed, resulting in the sustained proliferation and dissemination of tumour cells. As shown in Figure 1, meloxicam reactivates the apoptotic program of tumour cells by regulating the expression of apoptosis-related proteins, thereby providing a novel avenue for tumour treatment [2].

Meloxicam plays a significant role in the inhibition of tumour angiogenesis. Tumour growth and metastasis are dependent on an abundant blood supply, and tumour angiogenesis represents a critical process for providing this supply to tumours. Meloxicam has the capacity to impede the proliferation and migration of vascular endothelial cells by reducing the expression of vascular endothelial growth factor (VEGF), thereby effectively inhibiting tumour angiogenesis. This mechanism of action is of significant importance in terms of blocking the nutrient supply of tumours and limiting their growth and metastasis. By inhibiting tumour angiogenesis, meloxicam is able to impede tumour development at its source, thereby offering a novel strategy for tumour treatment [3].

Meloxicam has demonstrated favourable outcomes in immunomodulation. It has the capacity to regulate the function of immune cells within the tumour microenvironment, enhancing the efficacy of immune cells in targeting tumour cells. The tumour microenvironment is a complex ecosystem, in which the functional status of immune cells exerts a significant influence on the development of tumours and the efficacy of treatment. Meloxicam enhances the body's immune defence mechanism by regulating the function of immune cells, improving immune surveillance and the ability to kill tumour cells.

3. Pharmacokinetics

3.1. Absorption

Meloxicam is typically administered orally and is distinguished by its rapid absorption and high bioavailability, which enables the drug to enter the body and exert its effects within a relatively short timeframe. The absorption process of meloxicam is influenced by a range of factors, including abdominal pain, diarrhoea, and dyspepsia, which may interfere with its absorption [4]. These gastrointestinal discomforts may impact the dissolution, transit, and absorption process of the drug within the gastrointestinal tract. Abdominal discomfort may result in irregular gastrointestinal peristalsis, which could potentially alter the residence time and rate of absorption of the drug within the intestinal tract. Diarrhoea may also reduce the residence time of the drug within the intestinal tract, reducing the likelihood of absorption. Dyspepsia may influence the dissolution and release of the drug, which could subsequently affect the absorption process. Although the impact of food on meloxicam absorption is relatively minor, individual differences may still result in variations in absorption. There are some differences in the time to peak and peak concentration of meloxicam among individuals, suggesting that such individual differences may arise from a range of factors, including age, gender, body weight, genetic factors, physiological status, and coadministration of medications [5]. The gastrointestinal function of the elderly may be relatively impaired, potentially influencing drug absorption. Genetic variations among individuals may result in differential activities of drug-metabolising enzymes, consequently affecting the absorption and metabolism of the drug.

3.2. Distribution

Meloxicam is widely distributed throughout the body, with the potential to enter numerous tissues and organs. This property provides a foundation for its anti-tumour effect. Meloxicam exhibits a high plasma protein binding rate, which significantly influences the distribution and metabolism of the drug. The distribution of the drug is significantly influenced by factors such as its lipid solubility and

the plasma protein binding rate. A higher protein binding rate may result in a portion of meloxicam forming a tight bond with plasma proteins, which could potentially impact its free concentration and range of distribution within the body. The potential concern regarding the distribution of meloxicam in tumour tissues has been investigated [6]. The microenvironment of tumour tissues differs from that of normal tissues, and the distribution of meloxicam in tumour tissues is of crucial importance for its anti-tumour effects. If meloxicam can achieve a higher concentration in tumour tissues, it is more likely to effectively inhibit tumour cell growth, proliferation and metastasis. This also provides an important avenue for further research, with the aim of optimising the dosing regimen of meloxicam and improving its anti-tumour efficacy.

3.3. Metabolism

Meloxicam is primarily metabolised by the liver, with the cytochrome P450 enzyme system, particularly CYP2C9 and CYP3A4, exerting a pivotal influence on its metabolism. Genetic polymorphisms of enzymes such as CYP2C9 and CYP3A4 impact the rate of meloxicam metabolism in the liver, and specific individual genetic variants also result in alterations of metabolising enzyme activities, which subsequently affect the drug's metabolic rate. The pathophysiological status of tumour patients, including liver and renal function, tumour type and stage, can influence the pharmacokinetics of meloxicam [7]. The combination of drugs also affects the metabolism of meloxicam, and drug interactions must be considered in clinical practice. In general, drugs that interact with meloxicam and affect its metabolism include other drugs that are metabolised through the cytochrome P450 enzyme system. These include certain antiepileptic drugs, antiarrhythmic drugs, antibiotics, and some anticoagulants and antihypertensives [8].

3.4. Excretion

Meloxicam is metabolised by hydroxylation and further oxidation of some of the methyl groups of thiazoles to four biologically inactive metabolites, approximately half of which are excreted in the urine and the remainder in the faeces. The elimination half-life is approximately 20 h, with steady-state plasma concentrations being reached within 3-5 d. The elimination rate of meloxicam is relatively low. Meloxicam is excreted relatively slowly with a long half-life, which is closely related to the metabolism and excretion process of the drug. In patients with renal insufficiency, reduced excretion of the drug may occur, increasing the risk of accumulation in the body. In clinical practice, dosage adjustments or monitoring of drug concentration may be necessary for patients with renal insufficiency [9].

The existing studies have concentrated on the correlation between the dosage of meloxicam and pharmacokinetic variables, as well as the impact of diverse routes of administration on pharmacokinetics. Ziesenitz et al. investigated the pharmacokinetic attributes of meloxicam in specific populations, which serves as a crucial reference for the rational utilisation of the drug in clinical settings [10]. The elderly may exhibit diminished hepatic and renal functions, necessitating an adjustment of the dosage on an individual basis to circumvent adverse effects resulting from drug accumulation. The pharmacokinetic study of meloxicam, as an antineoplastic drug, is of paramount importance for the optimisation of the therapeutic regimen and the assurance of drug safety.

4. Safety evaluation

The safety assessment of meloxicam in anti-tumour therapy is primarily concerned with its potential for adverse reactions and events during prolonged use. Although meloxicam has been demonstrated to possess anti-tumour properties in a multitude of cancer models, its safety profile requires further comprehensive evaluation. The potential safety risks associated with meloxicam should not be overlooked solely on the basis of its anti-tumour efficacy [11].

Gastrointestinal reactions are a common adverse effect associated with meloxicam. Meloxicam exerts its pharmacological effects by inhibiting COX-2. This mechanism may potentially impair the

protective functions of the gastrointestinal mucosa. The gastrointestinal mucosa is frequently dependent on substances such as prostaglandins to maintain its integrity and normal function. The inhibition of COX-2 by meloxicam may reduce the production of these protective substances, increasing the risk of ulceration and bleeding. Although meloxicam has a relatively limited impact on the gastrointestinal tract in comparison to conventional non-selective NSAIDs, long-term use may still result in the onset of gastrointestinal adverse effects. Patients may present with symptoms such as gastric discomfort, nausea, vomiting, and dyspepsia. In severe cases, it may also result in gastrointestinal ulceration and haemorrhage, which can potentially be life-threatening. When meloxicam is employed for anti-tumour therapy, medical practitioners must exercise vigilance in monitoring the incidence of gastrointestinal symptoms and implement timely preventive and therapeutic measures as necessary [12].

Prolonged administration of meloxicam has been associated with adverse effects on liver and kidney function. This is of particular concern in patients with impaired liver function. The metabolism of meloxicam is largely dependent on hepatic cytochrome P450 enzymes. In the event of impaired liver function, the activity of these enzymes may be diminished, resulting in incomplete metabolism of meloxicam [13]. The incomplete metabolism of pharmaceuticals may result in their accumulation within the body, thereby increasing the risk of toxicity. Caution must be exercised when administering meloxicam to patients with impaired renal function. Meloxicam is primarily excreted through the kidneys, and patients with renal insufficiency exhibit a diminished capacity to excrete the drug, which may result in its accumulation within the body. Patients with renal insufficiency exhibit markedly elevated levels of meloxicam exposure, thereby exacerbating the risk of nephrotoxicity. Abnormal renal function indices, such as elevated serum creatinine and urea nitrogen, may be indicative of nephrotoxicity, which in severe cases may result in renal failure [14]. When administering meloxicam to patients with impaired hepatic or renal function, physicians must adjust the dosage of the drug in accordance with the patient's specific circumstances or select alternative, safer treatment options.

The long-term use of nonsteroidal anti-inflammatory drugs (NSAIDs), particularly COX-2 selective inhibitors, has been linked to an elevated risk of cardiovascular incidents, including myocardial infarction and stroke. Although meloxicam is associated with a reduced cardiovascular risk in comparison to other COX-2 inhibitors, there are studies that indicate that long-term use of the drug may contribute to an increased cardiovascular risk, particularly in patients with a history of cardiovascular disease. The mechanism by which meloxicam may contribute to adverse cardiovascular events may be related to its inhibitory effect on prostaglandin synthesis. Prostaglandins play a pivotal role in maintaining the normal functioning of the cardiovascular system, including the regulation of vascular tone and the inhibition of platelet aggregation. The inhibition of prostaglandin synthesis by meloxicam may result in the disruption of normal physiological functions, thereby increasing the risk of cardiovascular events. When meloxicam is employed for anti-tumour therapy, it is imperative that physicians conduct comprehensive assessments of the cardiovascular status of patients, exercise greater caution in administering meloxicam to those with a history of cardiovascular disease, and closely monitor any changes in cardiovascular indices [15].

In order to mitigate the adverse effects of meloxicam in anti-tumour therapy, the use of nanotechnology as a potential solution has been developed. The incorporation of meloxicam into nanocarriers facilitates the targeted delivery of the drug to the tumour site, thereby reducing systemic toxicity and enhancing safety. The key advantage of nanotechnology is its capacity to facilitate precise drug delivery. The use of appropriate nanocarriers enables the targeted delivery of meloxicam to tumour tissue, thereby reducing the distribution of the drug in normal tissues. This not only mitigates the adverse effects of the drug on normal tissues, but also increases the concentration of the drug in the tumour site, thereby enhancing its anti-tumour effect. The utilisation of nanotechnology not only prolongs the half-life of meloxicam within the body, but also mitigates the adverse effects on normal tissues. This results in the drug remaining in the body for a longer period of time while simultaneously exhibiting reduced toxicity to normal tissues. This optimisation of drug delivery

provides a new safety guarantee for the clinical application of meloxicam and offers patients a greater range of therapeutic options [16].

Meloxicam has the potential to be a valuable addition to anti-tumour therapy, but it is essential to be fully aware of the potential safety risks associated with its use. The principal adverse reactions associated with long-term meloxicam administration include gastrointestinal, hepatic and renal impairment, and cardiovascular adverse events. To guarantee patient safety, medical practitioners must closely monitor patients' signs and symptoms when administering meloxicam for anti-tumour therapy, and make prompt adjustments to the treatment regimen as necessary. The utilisation of innovative drug delivery techniques, such as nanotechnology, may offer novel insights and methodologies for the clinical deployment of meloxicam, thereby enhancing its safety and efficacy. Further studies are required to gain a deeper understanding of the mechanism of action and safety risks associated with meloxicam. This will provide a more scientific basis for its rational application in anti-tumour therapy.

5. Conclusion

Meloxicam has demonstrated enhanced therapeutic potential in the context of anti-tumour therapy in recent years. The anti-tumour mechanism of meloxicam has been the subject of relatively few studies. These studies have primarily focused on the inhibition of the COX-2/PGE2 signalling pathway, the regulation of apoptosis-related proteins, the inhibition of tumour angiogenesis and the regulation of immune function. The clinical pharmacokinetics of meloxicam is characterised by complete absorption when taken orally, with more than 99% of the drug bound to plasma proteins, and rarely excreted unmetabolised. Meloxicam has been shown to have a similar risk of adverse effects to other NSAIDs, including gastrointestinal, hepatic, and renal effects. However, the incidence of these effects is relatively low compared to traditional NSAIDs.

Despite recent advances in meloxicam anti-tumour research, numerous challenges remain to be addressed. There is a dearth of targeted studies on tumour patients. The majority of current pharmacokinetic studies of meloxicam are primarily focused on healthy volunteers or animal models, with a paucity of clinical studies on tumour patients. Individual differences are pronounced, and there are notable discrepancies in the pharmacokinetic parameters of meloxicam between individuals. There is a dearth of studies on the combination of meloxicam with other anti-tumour drugs. It is imperative that future clinical research on the pharmacokinetics of meloxicam in different tumour patients be intensified. This will facilitate the establishment of comprehensive kinetic models and enable a thorough investigation of the underlying mechanisms of individual differences, which may be attributed to genetic factors, physiological and pathological variations, and other factors. It is crucial to devote attention to the research and application of meloxicam co-administration with other oncology drugs and nanotechnology.

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