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Review Article

The Oxicams: Relevance in the Management of Human Diseases and their Quantification in Biological Matrices

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Abstract

Oxicams (enolic acid derivatives) are a group of structurally closely related substances. They are weakly acidic and extensively bound to plasma proteins. Their mechanisms of action involve inhibition of cyclooxygenase (COX) especially type II, a key enzyme in the biosynthesis of prostaglandins in the body as well as exerting potent and irreversible inhibitory effect on platelet aggregation leading to an increased risk of bleeding in patients. Clinically, they are highly potent therapeutic agents utilized in the management of a number of human body dysfunctions namely inflammation, stiffness, acute and chronic pain syndromes associated with ankylosing spondylitis, arthrosis, osteoarthritis, rheumatoid arthritis, arthritic diseases such as acute gout, bursitis, injuries, sprains, shoulder or hip periarthritis (shoulder-hand syndrome), and tendinitis. They are also employed for short-term treatment of postoperative and post-traumatic pain.

Quantification and/or detection of oxicams in biological matrices have been accomplished by various analytical techniques namely spectrophotometric, electrochemical, immunological, titrimetric, and chromatographic methods.

Keywords: *Oxicams; Physicochemical Properties; Therapeutic Properties; Detection and Quantification in Biological Matrices*

Introduction

Human disease is any deviation from normal state of health or wellness which can be mental, physical and social well-being leading to disruption or loss of homeostasis [1].

Oxicams are relatively new enolic acid class of 4-hydroxyl-1,2 benzothiazine carboxamide. The fused thiazine ring contains sulfur and nitrogen atoms in the core structure. They are weakly acidic (diprotic acids) having ionization constants (pKa) range from 3 to 6.

Oxicams act by inhibiting cyclooxygenase (COX) especially type II, a key enzyme in the biosynthesis of proinflammatory prostanoids such as prostaglandins in the body [2]. Cyclooxygenase is an enzyme that converts arachidonic acid into prostaglandins in inflammatory processes in humans [3,4]. As cyclooxygenase inhibitors, they can also exert potent and irreversible inhibitory effect on platelet aggregation leading to an increased risk of bleeding in patients [5]. Oxicams besides the inhibition of prostaglandins (PG) production, are also associated with caspase-3 and caspase-9 activation, tumor cell apoptosis induction, tumor cell proliferation inhibition, and anti-angiogenesis [6,7].

Clinically, they alleviate fever, pain, dental discomfort, chronic diseases such as rheumatoid arthritis, osteoarthritis, lower back pain, shoulder periarthritis, cervical-shoulder-wrist syndrome and inflammation linked to various conditions, including trauma, and surgery

[8-10]. They typically have high bioavailability making them highly potent agents. Oxicams are extensively bound to plasma proteins (> 97%) due to their favorable amphiphilic properties leading to increased persistence in the body and a high duration of action.

These therapeutic agents are associated with a number of severe side effects such as (i) gastrointestinal (ulcers, bleeding, gastric perforations), which constitute one-third of all adverse drug reactions [11]. For instance piroxicam (the first drug of the oxicam class) although a highly potent oxicam was taken off the market in some countries because of its greater propensity to cause these severe gastrointestinal side effects when compared to other oxicams, (ii) cardiovascular side effects such as myocardial infarction, heart burn, stroke [12].

Recent efforts have focused on reducing the severe gastrointestinal effects through prodrug approach [13]. For example, the replacement of piroxicam with piroxicam prodrugs (ampiroxicam, droxicam and piroxicam) has become an inevitable shift to reduce piroxicam-related gastrointestinal adverse effects and maximize patient benefit [14]. Furthermore, scientists in an effort to circumvent the adverse effects of these very potent therapeutic agents produced another class of anti-inflammatory and analgesic agents called selective COX-2 inhibitors (Coxibs) such as celecoxib rofecoxib, valdecoxib, parecoxib, and lumiracoxib. Unfortunately, the expectations were short-lived because almost all these selective COX-2 inhibitors were withdrawn from market globally due to their toxicities.

Extended plasma protein binding, oxicams may reduce the concentration of drug that is free to diffuse into tissues as well as cause drug safety issues and adverse effects such as low clearance, drug-drug interactions, loss of efficacy and therefore calls for plasma concentration measurement.

The measurement of plasma concentrations of oxicams given in therapy may be used to assess adherence to therapy, adjust the dose to individual need and to minimize the risk of dose-related adverse effects. Such plasma concentration measurement will require accurate, precise, sensitive, selective, and specific analytical techniques.

Purpose of the Study

The purpose of the study is to present the relevance of oxicams in the treatment of autoimmune diseases as well as other human ailments despite severe adverse effects associated with some of the active agents. Furthermore, the study examined some physicochemical properties of this class of therapeutic agents and different analytical techniques that have been used for their detections and quantifications in biological matrices.

Discussion

Oxicams that are of clinical importance are ampiroxicam, droxicam, isoxicam, lornoxicam, meloxicam, piroxicam, sudoxicam, tenoxicam. However, due to severe adverse effects such as fatal skin reactions associated with isoxicam and gastrointestinal bleeding, perforation and ulceration associated with piroxicam, both have been withdrawn from markets in some countries. Some of the physicochemical properties of oxicams include:

a) Ampiroxicam (piroxicam prodrug): chemically defined as Ethyl 1-({2-methyl-1,1-dioxo-3-[(pyridin-2-yl)carbamoyl]-2H-1lambda6,2-benzothiazin-4-yl}oxy)ethyl carbonate, the molecular formula is $C_{20}H_{21}N_3O_7S$, and molar mass of 447.46 g/mol. Practically insoluble in water and soluble in some organic solvents. The chemical structure is given below:

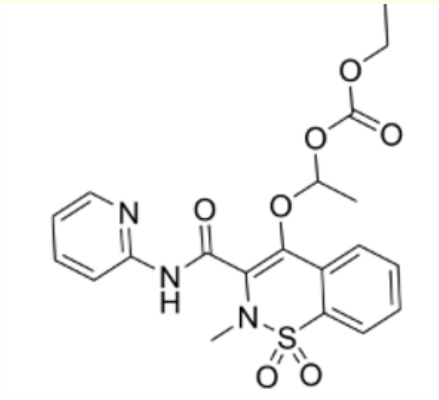

Figure 1: *Chemical structure ampiroxicam.*

b) Droxicam (piroxicam produg), chemically defined as 5-Methyl-3-(pyridin-2-yl)benzo[5,6][1,2]thiazino[3,4-e][1,3]oxazine-2,4(3H,5H)-dione 6,6-dioxide, the molecular formula is $C_{16}H_{11}N_3O_5S$, and molar mass of 357.34 g/mol. The chemical structure is given below:

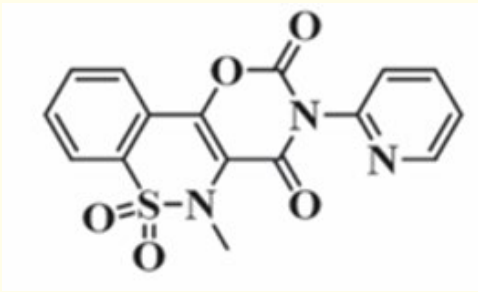

Figure 2: *Chemical structure of droxicam.*

c) Isoxicam, defined chemically as 4-hydroxy-2-methyl-N-(5-methyl-1,2-oxazol-3-yl)-1,1-dioxo-1λ⁶,2-benzothiazine-3-carboxamide, the molecular formula $C_{14}H_{13}N_3O_5S$ and molar mass of 335.34 g/mol. It is practically insoluble in water but soluble in some organic solvents. The chemical structure is given below:

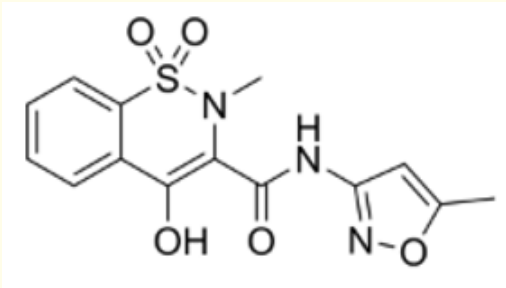

Figure 3: *Chemical structure isoxicam.*

d) Lornoxicam, chemically defined as (3E)-6-chloro-3-[hydroxy(pyridin-2-ylamino)methylene]-2-methyl-2,3-dihydro-4H-thieno[2,3-e][1,2]thiazin-4-one 1,1-dioxide, the molecular formula is $C_{13}H_{10}ClN_3O_4S_2$, and molar mass of 371.81 g/mol. The chemical structure is given below:

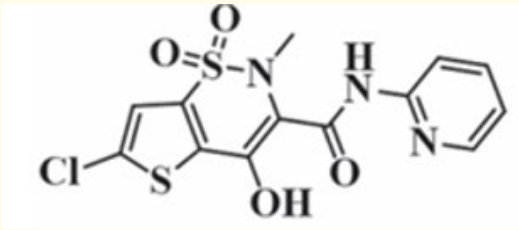

Figure 4: *Chemical structure of lornoxicam.*

e) Meloxicam, defined chemically as 4-hydroxy-2-methyl-N-(5-methyl-1,3-thiazol-2-yl)-2H-1,2 benzothiazine-3-carboxamide-1,1-dioxide, the molecular formula is $C_{14}H_{13}N_3O_4S_2$ and molar mass of 351.40 g/mol. The drug is practically insoluble in water, slightly soluble in acetone, soluble in dimethylformamide, very slightly soluble in ethanol and in methanol. The logarithm partition coefficient and ionization constant (pKa) are 1.16 and 4.47 respectively [15]. The chemical structure is given below:

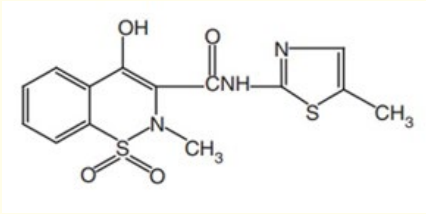

Figure 5: *Chemical structure of meloxicam.*

f) Piroxicam chemically defined as 1,2-benzothiazine-3-carboxamide-4-hydroxy-2-methyl-N-(2 pyridyl)-1,1-dioxide, the chemical formula is $C_{15}H_{13}N_3O_4S$ and molar mass of 331.35 g/mol. It is practically insoluble in water, soluble in methylene chloride, and slightly soluble in ethanol. The logarithm partition coefficient, ionization constant (pKa) are 3.06 and 6.30 respectively [15]. The chemical structure is given below:

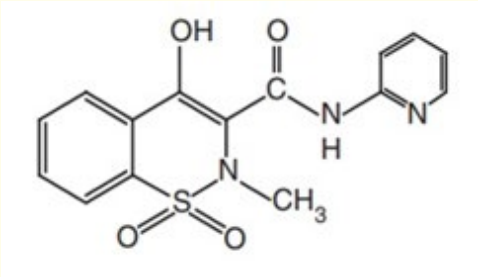

Figure 6: *Chemical structure of piroxicam.*

g) Sudoxicam chemically defined asN-(2-thiazolyl)-4-hyroxy-2-methyl-2H-1,2-benzothiazine-3-carboxamide 1,1-dioxide, the chemical formula is $C_{13}H_{11}N_3O_4S_2$ and molar mass of 337.37 g/mol. The chemical structure is given below:

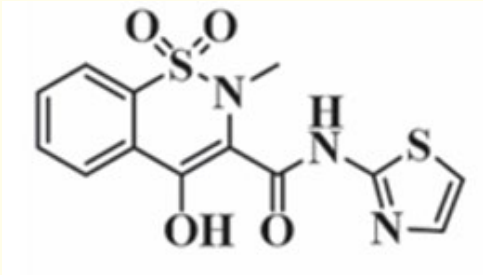

Figure 7: *Chemical structure of sudoxicam.*

h) Tenoxicam chemically defined as 4-hydroxy-2-methyl-N-(pyridin-2-yl)-2H-thieno[2,3-e] [1,2] thiazine-3-carboxamide 1,1-dioxide, its molecular formula is $C_{13}H_{11}N_3O_4S_2$, and molar mass of 337.37 g/mol. The drug is practically insoluble in water, sparingly soluble in methylene chloride, very slightly soluble in ethanol, and soluble in solutions of acids and alkalis. The logarithm partition coefficient, ionization constant (pKa) are 1.19 and 5.07 respectively [15]. The chemical structure is given below:

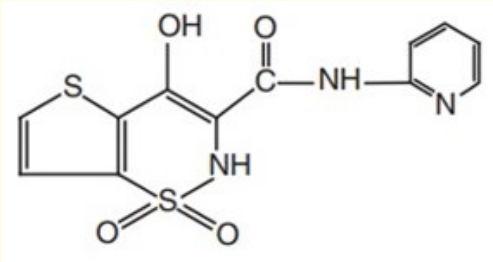

Figure 8: *Chemical structure of tenoxicam.*

The analytical techniques for detections and quantifications of oxicams

Different analytical techniques namely chromatography [high-performance liquid chromatography-UV detector (HPLC-UV), high performance liquid chromatography-fluorescence detector (HPLC-FD), high performance liquid chromatography-photo diode array detector (HPLC-PDA), high performance liquid chromatography-mass spectrometry (HPLC-MS), high performance liquid chromatography-tandem mass spectrometry (HPLC-MS/MS), ultra-high performance liquid chromatography-tandem mass spectrophotometry (UHPLC-MS/MS), supercritical fluid chromatography (SFC), gas chromatography flame ionization detector (GC-FID), gas chromatography-mass spectrometry (GC MS), gas chromatography-tandem mass spectrometry (GC–MS/MS), liquid chromatography-high resolution mass spectrometry (LC-HRMS), and hydrophilic liquid chromatography (HILIC)]; capillary electrophoresis (capillary zone electrophoresis and micellar electrokinetic capillary chromatography); electrochemical (potentiometric and voltammetric techniques); immunological (enzyme-linked immunosorbent assay, immunochromatographic strip); spectrophotometry (spectrophotometric, fluorescence spectrophotometric, flow injection spectrophotometric); and titrimetry (non-aqueous) techniques could be utilized to determine these oxicams in pharmaceutical formulations and biological matrices [16-19].

Due to the long-term side effects of oxicams that are associated with gastrointestinal and cardiovascular complications, their determinations in biological matrices have gained increasing popularity [20]. Amongst the different analytical techniques enumerated, chromatographic techniques are the most widely used in the detection and quantification of these therapeutic agents in biological matrices. Such chromatographic techniques include:

(i) Non-hyphenated liquid chromatography:

(a) Plasma [21-25]; (b) urine: [26,27]; (c) bile: [28].

(ii) Hyphenated liquid chromatography:

(a) Whole blood: [29]; (b) plasma: [29-31]; (c) serum: [32]; (d) saliva: [31]; (e) erythrocytes: [29].

In general, liquid chromatography (hyphenated or non-hyphenated) although expensive, but due to its accuracy, sensitivity specificity is the analytical technique of interest to detect and quantify oxicams concentrations in biological matrices.

Conclusion

Oxicams are long-acting class of non-steroidal anti-inflammatory drugs (NSAIDs) with potent therapeutic effects against acute and chronic pain syndromes of various origins, especially vertebrogenic and joint pain. The mechanisms of action involve inhibiting the activity of cyclooxygenase enzymes involved in the synthesis of biological mediators in the cell, namely prostaglandins (involved in inflammation), and thromboxanes (involved in blood clotting). Hyphenated liquid chromatographic technique is the analytical method of interest in the detection and quantification of oxicams in biological matrices. Finally, the vast biological activities namely anti inflammatory, antipyretic, analgesic, antitumour, as well as their widely utilization to alleviate debilitating conditions such as gout, rheumatoid arthritis, osteoarthritis, migraines, menstrual irregularities, and postoperative complications make oxicams highly relevant in the management of human diseases.

Bibliography

1. Loscalzo J., *et al*. "Human disease classification in the postgenomic era: a complex systems approach to human pathobiology". *Molecular Systems Biology* 3 (2007): 124-128.

2. Gouda MA., *et al*. "Synthesis and Medicinal importance of oxicams and their analogues". *Synthetic Communications* 47.19 (2017): 1709-1736.

3. Flower R., *et al*. "Effects of anti-inflammatory drugs on prostaglandin biosynthesis". *Nature New Biology* 238 (1972): 104-106.

4. Warner TD and Mitchell JA. "Cyclooxygenases: new forms, new inhibitors, and lessons from the clinic". *FASEB Journal* 18.7 (2004): 790-804.

5. Olsen S., *et al*. "Association of NSAID use with risk of bleeding and cardiovascular events in patients receiving antithrombotic therapy after myocardial infarction". *JAMA* 313.8 (2015): 805-814.

6. Gordon MW., *et al*. "Regulation of p53-targeting microRNAs by polycyclic aromatic hydrocarbons: implications in the etiology of multiple myeloma". *Molecular Carcinogenesis* 54.10 (2015): 1060-1069.

7. Goto T., *et al*. "Administration of nonsteroidal anti-inflammatory drugs accelerates spontaneous healing of osteoid osteoma". *Archives of Orthopedic and Trauma Surgery* 131.5 (2011): 619-625.

8. Izadi P., *et al*. "Non-steroidal anti-inflammatory drugs in the environment: Where were we and how far we have come?" *Environmental Pollution* 267 (2020): 115370.

9. Kelley BP., *et al*. "Management of acute postoperative pain in hand surgery: a systematic review". *Journal of Hand Surgery* 40.8 (2015): 1610-1619.

10. Sai S., *et al*. "Preoperative ampiroxicam reduces postoperative pain after hand surgery". *Journal of Hand Surgery* 26.4 (2001): 377-379.

11. Walters KM and Woessner KM. "An overview of nonsteroidal antiinflammatory drug reactions". *Immunology and Allergy Clinics of North America* 36.4 (2016): 625-641.

12. Mukherjee D., *et al*. "Risk of cardiovascular events associated with selective COX-2 inhibitors". *JAMA* 286.8 (2001): 954-959.

13. Sehajpal S., *et al*. "Prodrugs of non-steroidal anti inflammatory drugs (NSAIDs): a long march towards synthesis of safer NSAIDs". *Mini Reviews in Medicinal Chemistry* 18.14 (2018): 1199-1219.

14. Olkkola KT., *et al*. "Pharmacokinetics of oxicam nonsteroidal anti inflammatory agents". *Clinical Pharmokinetics* 26.2 (1994): 107-120.

15. Parikh NH., *et al*. "Analytical methods for quantification of non-steroidal anti-inflammatory drugs in pharmaceutical and biological samples: An overview of developments in the last decade". *Arabian Journal of Chemistry* 17.1 (2024): 105446.

16. Al-Momani IF. "Indirect low-injection spectrophotometric determination of meloxicam, tenoxicam and piroxicam in pharmaceutical formulations". *Analytical Science* 22.12 (2006): 1611-1614.

17. El-Ries MA., *et al*. "Spectrophotometric and potentiometric determination of piroxicam and tenoxicam in pharmaceutical preparations". *Chemical and Pharmaceutical Bulletin* 51.1 (2003): 6-10.

18. Lin L., *et al*. "Ultrasensitive and simultaneous detection of 6 nonsteroidal anti-inflammatory drugs by colloidal gold strip sensor". *Journal of Dairy Science* 104.3 (2021): 2529-2538.

19. El Walily AFM., *et al*. "Simultaneous determination of tenoxicam and 2-aminopyridine using derivative spectrophotometry and high-performance liquid chromatography". *Journal of Pharmaceutical and Biomedical Analysis* 15.12 (1997): 1923-1928.

20. Martinez-Sena T., *et al*. "Determination of non-steroidal anti inflammatory drugs in water and urine using selective molecular imprinted polymer extraction and liquid chromatography". *Journal of Pharmaceutical and Biomedical Analysis* 131 (2016): 48-53.

21. Munera-Jaramillo MI and Botero-Garces S. "Determination of tenoxicam in plasma by high-performance liquid chromatography". *Journal of Chromatography: Biomedical Science and Application* 616.2 (1993): 349-352.

22. Emara L., *et al*. "A simple and sensitive HPLC/UV method for determination of meloxicam in human plasma for bioavailability and bioequivalence studies". *Journal of Applied Pharmaceutical Science* 6.7 (2016): 012-019.

23. Wanwimolruk S., *et al*. "A simple and sensitive HPLC assay for piroxicam in plasma and its application to bioavailability study". *Journal of Liquid Chromatography* 14.12 (1991): 2373-2381.

24. Sora I., *et al*. "Fast RPLC-UV method on short sub-two micron particles packed column for the assay of tenoxicam in plasma samples". *Journal of Pharmaceutical and Biomedical Analysis* 43.4 (2007): 1437-1443.

25. Mason JL and Hobbs GJ. "Simple method for the analysis of tenoxicam in human plasma using high-performance liquid chromatography". *Journal of Chromatography B: Biomedical Sciences and Application* 665.2 (1995): 410-415.

26. Manousi N., *et al*. "Salt-induced homogeneous liquid-liquid microextraction of piroxicam and meloxicam from human urine prior to their determination by HPLC DAD". *Applied Science* 12.13 (2022): 6658.

27. Avgerinos A., *et al*. "Extractionless high-performance liquid chromatographic method for the simultaneous determination of piroxicam and 5′-hydroxypiroxicam in human plasma and urine". *Journal of Chromatography B: Biomedical Sciences and Application* 673.1 (1995): 142-146.

28. Milligan PA. "Determination of piroxicam and its major metabolites in the plasma, urine and bile of humans by high-performance liquid chromatography". *Journal of Chromatography B: Biomedical Science and Application* 576 (1992): 121-128.

29. Sultan M., *et al*. "Sample pretreatment and determination of non-steroidal anti-inflammatory drugs (NSAIDs) in pharmaceutical formulations and biological samples (blood, plasma, erythrocytes) by HPLC-UV-MS and micro-HPLC". *Current Medicinal Chemistry* 12.5 (2005): 573-588.

30. Ji HY., *et al*. "Simultaneous determination of piroxicam, meloxicam and tenoxicam in human plasma by liquid chromatography with tandem mass spectrometry". *Journal of Chromatography B: Analytical Technology Biomedical Life Science* 826.1-2 (2005): 214-219.

31. Calvo AM., *et al*. "Quantification of piroxicam and 5′-hydroxypiroxicam in human plasma and saliva using liquid chromatography-tandem mass spectrometry following oral administration". *Journal of Pharmaceutical and Biomedical Analysis* 120 (2016): 212-220.

32. Shirako J., *et al*. "Simultaneous determination for oxicam non-steroidal anti-inflammatory drugs in human serum by liquid chromatography-tandem mass spectrometry". *Forensic Science International* 227.1-3 (2013): 100-102.

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