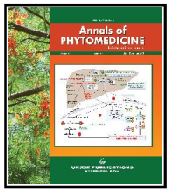
Annals of Phytomedicine 12(2): 266-269, 2023

DOI: http://dx.doi.org/10.54085/ap.2023.12.2.31

Annals of Phytomedicine: An International Journal

http://www.ukaazpublications.com/publications/index.php

Print ISSN : 2278-9839 Online ISSN : 2393-9885



Review Article : Open Access

A systematic review of lumefantrine

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Article Info

Article history

Received 1 November 2023

Revised 19 December 2023

Accepted 20 December 2023

Published Online 30 December 2023

Keywords

Lumefantrine

Metabolism

Malaria

Pharmacokinetics

Abstract

One of the most important ingredients in artemisinin-based combination therapies (ACTs), lumefantrine, has become a vital weapon in the global fight against malaria. The pharmacological characteristics of lumefantrine, such as its metabolism, pharmacokinetics, and mechanism of action, are thoroughly examined in this review. In treating simple *Plasmodium falciparum* malaria, the study examines the clinical effectiveness and safety profile of lumefantrine, providing insight into how it works to prevent resistance and guarantee treatment success. The review also covers issues like dosing schedules, adherence, and possible drug interactions that arise when using lumefantrine. Lumefantrine is important in the current antimalarial strategies; insights into ongoing research and future directions for optimizing its therapeutic impact are also addressed.

1. Introduction

The synthetic antimalarial drug lumefantrine has emerged as a key component of the international response against *Plasmodium falciparum* malaria. Lumefantrine is a medication that was created to work in conjunction with combination treatments based on artemisinin (ACTs) to fight malaria parasites that are resistant to multiple drugs. This compound has strong schizonticidal activity and is a member of the aryl amino alcohol class (Akella Anuradha *et al.,* 2023; Prathyusha, 2022).

Lumefantrine was first prescribed in conjunction with artemether, and it has proven to be remarkably effective in treating simple cases of malaria, particularly in regions where immunity against other antimalarial medications has spread. The effectiveness of lumefantrine as a medication is largely dependent on its pharmacological characteristics, which include its metabolism, pharmacokinetics, and mode of action. Because lumefantrine is a lipophilic substance, it is better absorbed when taken with fatty meals, which highlights the significance of the right dosage circumstances.

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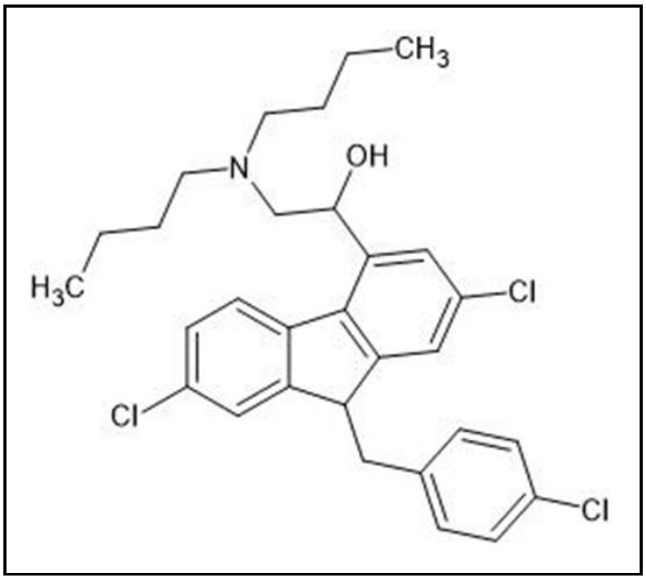

Figure 1: Structural formula of lumefantrine.

1.1 Dose

Lumefantrine is typically administered over three days in six doses. The number of tablets you should take each dose should be carefully followed by you and your doctor. Doses of lumefantrine are determined by age and weight.

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1.2 Physicochemical properties

1.3 Chemical structure

The chemical structure of lumefantrine is complex, with an aryl amino alcohol backbone. It is frequently found in a racemic mixture.

1.4 Molecular weight

Lumefantrine has a molecular weight of roughly 528.79 g/mol.

1.5 Solubility

Lumefantrine is lipophilic, meaning that it is poorly soluble in water and that its absorption is greatly increased when taken with fatty meals.

1.6 Melting point

Lumefantrine melts at a temperature between 117-120°C.

1.7 Partition coefficient (log P)

The lipophilicity of lumefantrine is indicated by the logarithm of the partition coefficient (log P), which highlights its preference for lipid-rich environments.

1.8 pKa (acid dissolution constant)

Due to its weak base nature, lumefantrine pKa is frequently poorly reported in the literature**.**

1.9 Stability

Under typical storage circumstances, lumefantrine is usually stable, but in the presence of light and moisture, it could degrade.

1.10 Appearance

Typically, lumefantrine is found as a crystalline powder that ranges from white to yellow (Vimal Raj and Sumithra, 2023; Nivetha *et al*., 2023).

1.11 Medicinal uses

Lumefantrine is an essential part of artemisinin-based combination therapies (ACTs) and is mainly used for its antimalarial qualities. These are some of its therapeutic applications:

1.11.1 Treatment of malaria

Lumefantrine is used as a first-line treatment for uncomplicated malaria caused by *Plasmodium falciparum*, including drug-resistant strains, in conjunction with derivatives of artemisinin, such as artemether (Aaisha Ansari *et al*., 2020).

1.11.2 Artemisinin-based combination therapies (ACTs)

An essential part of ACTs, lumefantrine is what the world health organization (WHO) suggests as the first line of treatment for malaria. A fast-acting derivative of artemisinin combined with lumefantrine has a synergistic effect that ensures quick parasite clearance and lowers the possibility of resistance building (Jahnavi Bandla and Ashok Gorja, 2022).

1.11.3 Prevention of recrudescence

Because of its comparatively long half-life, lumefantrine helps to keep the parasite from resurfacing during treatment, also known as recrudescence.

1.11.4 Adverse drug reactions

Common adverse drug reactions associated with lumefantrine use include.

1.11.5 Gastrointestinal disturbances

Among the side effects mentioned are nausea and vomiting. There may be discomfort or pain in the abdomen.

1.11.6 Central nervous system effects

Certain people have reported experiencing headaches and dizziness.

1.11.7 Cardiovascular effects

There have been reports of QT interval prolongation on electrocardiograms (ECGs), particularly at higher dosages.

1.11.8 Hepatic effects

Despite the rarity of severe hepatic reactions, elevated liver enzymes can happen.

1.11.9 Allergic reactions

There have been reports of allergic reactions, including skin rashes and itching.

1.11.10 Hematologic effects

There have been a few reported cases of neutropenia or a decrease in white blood cell count.

1.11.11 Other general side effects

Fatigue and weakness (Tayade and Nagarsenker, 2007).

2. Interactions

When lumefantrine and amprenavir are combined, their metabolisms may be slowed down. Combining antegrade with lumefantrine may make QTc prolongation more likely or more severe. When combined, antazoline and lumefantrine may make QTc prolongation more common or severe.

2.1 QT prolongation agents

There is a correlation between lumefantrine and prolonged QT interval. The risk of cardiac arrhythmias may increase if this medication is taken concurrently with other medications that also prolong the QT interval, such as some antipsychotics and antiarrhythmics.

2.2 Antimalarial interactions

Lumefantrine may not provide any additional therapeutic benefits and may even increase the risk of side effects when combined with other antimalarial medications, particularly those with similar mechanisms of action (Mohammed Zafar *et al*., 2020).

2.3 Food interactions

The absorption of lumefantrine is improved when consumed with high-fat meals. Consequently, to maximize lumefantrine's bioavailability, it is advised to take it with food.

2.4 CYP3A4 inducer/interactions

The cytochrome P450 enzyme system, in particular CYP3A4, metabolizes lumefantrine. CYP3A4-inducing or inhibiting drugs may affect lumefantrine levels. While inhibitors can raise lumefantrine

concentration and possibly cause toxicity, inducers may decrease lumefantrine efficacy (Varuni *et al.,* 2023).

3. Mechanism of action

Lumefantrine's precise mode of action to prevent malaria is unclear. Based on the available data, it appears that lumefantrine inhibits protein and nucleic acid synthesis as well as the formation of β-hematin by forming a complex with hemin. It involves the production of cytotoxic radical species as a result of an interaction with ferriprotoporphyrin IX ("heme"), or ferrous ions, in the acidic parasite food vacuole. The widely acknowledged mode of action of peroxide-containing antimalarial drugs entails the drug's interaction with heme, a hemoglobin degradation byproduct obtained from hemoglobin's proteolysis. It is thought that a variety of potentially harmful oxygen and carbon-centered radicals are formed as a result of this interaction (Shaimaa Fayez *et al*., 2018; Sujatha Samala *et al*., 2022).

4. Analytical methods for lumefantrine

Recent guidelines from the world health organization (WHO) recommend treating uncomplicated falciparum malaria with artemisinin-based combination therapy (ACT). Artemether and lumefantrine is an ACT that was prequalified by the WHO for efficacy, safety, and quality, and it was recently approved by the USA-FDA. Swiss medic had also approved it in December 2008. Lumefantrine and artemether come in a fixed-dose formulation called coartem. Its two parts work in concert to produce synergistic antimalarial activity through their distinct mechanisms of action. It can be used to treat adults, children, and newborns that have a simple, acute infection caused by *Plasmodium falciparum* or a combination of diseases involving falciparum administration is made simple with court dispersible, a formulation with enhanced palatability designed especially for children that dissolve fast in a minimal amount of water. The six-dose artemether and lumefantrine combination is effective in a variety of patient demographics worldwide (Michael Makanga, 2002**)**.

Regarding the purpose of estimating both pure and medicinal dose versions of artemether and lumefantrine, a straightforward and accurate HPLC method was created. In an isocratic mode, the quantification was performed with symmetry C18, 250 x 4.6 millimeters and a particle size of 5 µm. The period of mobility involved compressing buffer about acetonitrile of 40:60 (v/v), at a pH of 3 ± 0.5, 1.5 ml/min was the flow rate, and a dual UV detector 210 and 303 nm was used for detection. For artemether and lumefantrine, the durations of retention were 13.887 and 7.218 min, in that order. The recovery percentages for artemether and lumefantrine were determined to be 98.87 and 99.78%, respectively. The method was validated by evaluating multiple parameters (Sunil *et al.,* 2010).

Plasmodium falciparum is the deadly parasite that causes cerebral malaria (CM), a disease primarily affecting immunocompromised individuals. For CM, a combination of lumefantrine (LMF) and artemether (AM) is recommended as the first-line treatment. Since AM is a UV-inactive molecule, it can be difficult to evaluate large quantities using a standard procedure. Many applications and analytical difficulties with AM-LMF necessitate the creation of an easy-to-use, reliable, and affordable method for estimating AM and LMF simultaneously. Using n-hexane as the mobile phase ethyl acetate (8:2 v/v) an effective chromatographic separation of AM and LMF was achieved. The samples showed high linearity within the concentration range of 25-800 ng/spot for AM and 10-800 ng/spot for LMF. During validation studies, high levels of precision, robustness, ruggedness, sensitivity, and accuracy were noted **(**Ripandeep Kaur *et al*., 2021).

Within the framework of post-marketing surveillance, which aids public health authorities in making evidence-based choices to combat the proliferation of substandard pharmaceuticals, the Democratic Republic of the Congo (DRC) evaluated the quality of antimalarial artemether-lumefantrine (AL) medications. Due to the presence of either one or neither of the two reported active pharmaceutical ingredients (APIs), four samples (2.7%) failed the TLC test. 46 (30.7%) samples had artemether concentrations below 90% and 17 (11.3%) samples had artemether contents exceeding 110% of the quantity stated on the label, according to HPLC tests. Eight (5.3%) samples showed lumefantrine values above 110%, while 32 (21.7%) samples had lumefantrine contents below 90%. This DRC survey provides evidence of the widespread availability of low-quality antimalarial medications. The study, which uses three detection techniques, highlights the need to provide underdeveloped nations with access to contemporary methods like HPLC.

Lumefantrine and its metabolite dibutyl lumefantrine were simultaneously determined in human plasma using an RP-HPLC-UV method that was designed to be straightforward, specific, precise, and fast. Standard protocols were followed in the optimization of the experimental parameters and the method's validation. The supelco discovery HS C18 RP (150 mm × 4.6 mm, 5 µm) column, with acetonitrile and 0.05% trifluoroacetic acid (70:30, v/v) as the mobile phase, produced the best resolution when pumped at a flow rate of 1.0 ml/min and wavelength of 335 nm. The method demonstrated adequate separation for lumefantrine and desbutyl lumefantrine. Lumefantrine's lower limit of detection (LLOD) and lower limit of quantification (LLOQ) were 10.0 and 18.0 ng/ml, respectively, while desbutyl lumefantrine's values were 7.5 and 15.0 ng/ml (Yasar Shah, 2019).

5. Conclusion

In conclusion, when employed in combination therapies, lumefantrine is essential to the treatment of malaria. It works by interfering with the lifespan of the malaria parasite, which has the beneficial effect of suppressing and curing the infection. To guarantee efficacy and reduce the chance of resistance, however, treatment course completion and adherence to recommended dosages are crucial. It is recommended to speak with a healthcare provider for specific advice and information about using lumefantrine.

Acknowledgments

The authors are very much thankful to the Management of Vels Institute of Science, Technology and Advanced Studies (VISTAS), Pallavaram, Chennai for providing fulfillment of all facilities for completion of this review article.

Conflict of interest

The authors declare no conflicts of interest relevant to this article.

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Citation **P. Shanmugasundaram, S. Harshini and G. Nithish Kumar (2023). A systematic review of lumefantrine. Ann. Phytomed., 12(2):266-269. http://dx.doi.org/10.54085/ap.2023.12.2.31.**