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Case Report

Artesunate/Amodiaquine and Risk of Vision Disorders: a Case Series

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Abstract

Aim: Artesunate/Amodiaquine tablet, when used at normal therapeutic doses, is not known to cause any form of vision disorder as evidenced by review of current medical literature including the summary of product characteristics. Amodiaquine alone, however, when taken at overdose or for relatively longer treatment durations has been associated with retinal and corneal disorders. The Eritrean Pharmacovigilance Centre has recently received five cases of vision disorders associated with a three-day treatment course of artesunate/amodiaquine combination tablet. The main objective of this study is therefore to investigate the possible causal relationship between artesunate/amodiaquine and vision disorders.

Methods: Search was made on the WHO global individual case safety reports database (October 15, 2018) using 'amodiaquine/aretsunate' as a drug substance and 'vision disorders' as a reaction term. In addition, all cases with extrapyramidal symptoms were excluded from this study to control confounders and avoid misclassification bias.

Results: Since 2006, a total of 28 cases of vision disorders associated with artesunate/amodiaquine have been reported. Artesunate/Amodiaquine was the sole drug administered in 39.28% of the cases. In six cases, vision problems abated following withdrawal of artesunate/amodiaquine and reaction recurred in one case after re-introduction of the suspected drug. Vision disorders were marked as 'serious' in 13 cases and outcome with total disability was noted in one case.

Conclusion: There appears to be a causal relationship between the three-day therapeutic doses of artesunate/amodiaquine and vision disorders. Therefore, close monitoring of patients for any vision disorder while on artesunate/amodiaquine treatment is recommended.

Keywords: *Artesunate/Amodiaquine; Vision Disorders; VigiBase; WHO Global Individual Case Safety Repots Database*

Abbreviations

ADR: Adverse Drug Reaction; AS/AQ: Artesunate/Amodiaquine; HCQ: Hydroxychloroquine; HLGT: High Level Group Term; IC: Information Component; MedDRA: Medical Dictionary for Regulatory Activities; RPE: Retinal Pigment Epithelial; SPC: Summary of Product Characteristics

Introduction

Artesunate/Amodiaquine (AS/AQ) fixed-dose combination tablet, an effective artemisinin-based anti-malarial therapy is not known to cause any vision disorder or ocular toxicity when used at normal therapeutic doses. The association is also not documented in the product

information leaflet and Summary of Product Characteristics (SPC) of Sanofi Aventis, the innovator company for Artesunate/Amodiaquine [1]. There was only a mention of possibility of eye discoloration following use of AS/AQ in the SPC. To the best of the authors' knowledge, there is only one published case report of a reversible binocular visual loss following concurrent use of AS/AQ and mefloquine chemoprophylaxis tablets [2].

Previously, amodiaquine had been used for the treatment of chronic discoid lupus erythematosus. With that treatment course, there is a published case report of a patient that presented with partial blindness due to acute changes in both corneas [3]. Another published case report documented diffuse conjunctival and corneal changes and abnormal retinal function tests following use of amodiaquine hydrochloride 250 mg taken as anti-pain for a one-year course [4]. McGuire., *et al.* also reported depression of retinal function in four of five previously clinically healthy subjects after daily intake of amodiaquine 200 mg for one month [5]. The SPC of the WHO pre-qualified AS/AQ of Guilin [6], IPC [7] and CIPLA [8], which might be based on the above publications, mention transient accommodation disorders, corneal opacifications and vision disorders following overdose and prolonged use of amodiaquine alone when taken for other indications.

Except for the aforementioned case report [2]; AS/AQ when used at therapeutic doses for the treatment of uncomplicated malaria, have never been associated with vision disorders. The Eritrean Pharmacovigilance Centre has however received five cases of vision disorders following a three-day course of AS/AQ taken for the treatment of uncomplicated malaria. The purpose of this assessment is thus to assess the causal relationship of short therapeutic doses of AS/AQ and vision disorders.

Methods

Study design and data source

This is a descriptive case series assessment of vision disorders associated with the use of AS/AQ. The WHO global individual case safety reports database, VigiBase™, is used as a data source. VigiBase™, developed and maintained by the Uppsala Monitoring Centre, Sweden, is the world's largest database of its kind with about 19 million reports of adverse drug reactions and other related problems submitted from over 130-member states [9].

Study population

Patients who developed any form of vision disorder following the use of AS/AQ and who subsequently were submitted to the VigiBase™ by different member states are the study population for this study. Cases of visual disturbances co-reported with extrapyramidal symptoms (including muscle spasm, musculoskeletal stiffness, and gaze palsy) are excluded from the study to minimize outcome misclassification bias. This is because oculogyric crisis and/or eye gaze disturbances related to extrapyramidal symptoms may be grossly diagnosed by reporters as vision disorders. Cases that developed vision disorders following prolonged use of amodiaquine alone are also excluded from this study as the aim is to assess the causal relationship of vision disorders and AS/AQ used for relatively short treatment courses (not more than three days).

Exposure and outcome definition

The main exposure of interest of this study is AS/AQ provided to all age groups within normal therapeutic dosage ranges taken for a maximum of a three-day course. In addition to AS/AQ, other concurrently used drugs were considered. The primary outcome of this study is any form of vision disorder experienced following the use of AS/AQ.

Data retrieval approach

Search was made on the global individual case safety reports database, VigiBase™, on October 15, 2018 using 'vision disorders' as MedDRA reaction term and 'artesunate; amodiaquine' as active drug substance. The retrieved data was exported to excel spreadsheet for further descriptive analysis. To keep patients' and reporters' data confidential, the mining and analysis tool (VigiLyze) automatically excludes patients' and healthcare professionals' identifiers during retrieval. The series of cases were then subjected to causality assessment

using Hill's criteria [10]. Information component (IC value), a measure of disproportionality of drug– adverse reaction pair in the global database [11,12] was also automatically calculated using VigiLyze. A positive IC value indicates that a particular drug-adverse reaction pair is reported more often than expected, based on all the reports in VigiBase™.

Results

As of October 15, 2018, a total of 32 cases of vision disorders associated with AS/AQ were identified from six African countries. In four of the cases, extrapyramidal symptoms were co-reported with vision disorders and were thus, excluded from this study. The cases were submitted from the Democratic Republic of Congo (16), Ghana (6), Eritrea (5), Nigeria (2), Mozambique (2) and Senegal (1). The vision disorders reported following the use of AS/AQ are blurred vision (19), vision impairment (7), blindness (1) and transient blindness (1). Age was documented in 27 of the 28 cases and the median age was found to be 28 years (range: 4 - 81). The cases included 16 males and 12 females. Detailed description of the cases is summarized in table 1.

Case	Sex/ Age	Suspected(S), or Concomitant(C) drugs	Daily dose of AS/AQ	Reactions (MedDRA preferred terms)	Time to reaction onset (days)	Seriousness of the cases	Action taken/ outcome
1	F/17	AS/AQ(s), Doxycycline(s), Paracetamol(c), Iron(C)		Vision blurred, chest pain	1	Yes	-
2	F/23	Metoclopramide(s), AS/ AQ(c)	812 mg once daily	Visual impairment	3	Yes	None/Not recovered
3	M/23	AS/AQ(s)	812 mg once daily	Visual impairment, Salivary hypersecretion	1	Unknown	None/ Recovered
4	F/51	AS/AQ(s), Albendazole(c), Paracetamol(c)	-	Asthenia, Vision blurred	3	Unknown	None/ Recovering
5	M/30	AS/AQ(s)	812 mg once daily	Dizziness, Asthenia, Vision blurred	1	Unknown	None/ Recovered
6	M	AS/AQ(s)	812 mg once daily	Asthenia, Dizziness, Vision blurred	3	Unknown	None/ Recovered
7	M/64	AS/AQ(s)	2DF once daily	Fatigue, Vision blurred, Dizziness	2	Unknown	None/ Recovered
8	M/64	AS/AQ(s), Paracetamol(c)	2DF once daily	Visual impairment, Dizziness	1	Unknown	Drug with-drawn/ Recovered
9	M/28	AS/AQ(s), Paracetamol(c)	370mg twice daily	Vision blurred, Vomiting, Hallucination	1	Unknown	Dug with-drawn/ Not recovered
10	F/16	AS/AQ(s), Paracetamol(c)	2DF once daily	Visual impairment, Asthenia	1	Yes	None/ Recovered
11	M/33	AS/AQ(s), Ibuprofen(c)	2DF twice daily	Asthenia, Hyperhidrosis, Vision blurred	4	Yes	None/ Recovered
12	M/12	AS/AQ(s),	-	Visual impairment	1	Yes	Drug with-drawn/ Recovered
13	F/62	Nifurtimox(s), AS/ AQ(c), Eflornithine(c), Diazepam(c)	-	Diarrhoea, Back pain, Asthenia, Insomnia, Vision blurred	9	Unknown	Unknown/ Recovered

14	F/20	AS/AQ(s), Cefixime(c), Pyrantel(c)	2DF once daily	Headache, Asthenia, Vision blurred, Dizziness	4	Unknown	Drug withdrawn/ Recovered
15	F/23	AS/AQ(s), Cefixime(s), Paracetamol(s)	2DF once daily	Vomiting, Asthenia, Vision blurred, Dizziness	1	Unknown	None/ Recovered
16	F/19	AS/AQ(s)	2DF once daily	Asthenia, Vision blurred, Dizziness	2	Yes	None/ Recovered
17	F/33	AS/AQ(s), Paracetamol(c)	1DF twice daily	Chills, Headache, Insomnia, Fatigue, Vision blurred, Salivary hypersecretion, Conjunctival disorder	1	Yes	None/ Recovering
18	M/45	Primaquine(s), AS/AQ(c)	740 mg once daily	Visual impairment	3	Yes	None/Not recovered
19	F/46	AS/AQ(s), Unknown(s), Paracetamol(c), Multivitamin(c)	2DF once daily	Asthenia, Nausea, Pruritus, Hypotension, Vision blurred	4	Unknown	None / Unknown
20	M/04	AS/AQ(s), Primaquine(s), Metoclopramide(c)	370 mg once daily	Blindness	4	Yes	None/Not recovered
21	F/16	AS/AQ(s), Paracetamol(c), Pyrimethamine; Sulfadoxine(c)	-	Somnolence, Vision blurred, Gait disturbance	1	Unknown	None/ Recovered
22	M/30	AS/AQ(s)	-	Insomnia, Vision blurred, Pyrexia, Malaise, Fatigue, Heart stroke	1	Unknown	None/ Recovered
23	M/61	AS/AQ(s)	800 mg once daily	Malaise, Asthenia, Insomnia, Decreased appetite, Visual impairment	1	Unknown	Drug withdrawn/ Unknown
24	M/23	AS/AQ(s)	-	Seizure, Vision blurred, Circulatory collapse	2	Yes	None/ Recovered
25	M/81	AS/AQ(s)	-	Dizziness, Discomfort, Decreased appetite, Vision blurred, Asthenia	2	Unknown	None/ Recovered
26	M/58	AS/AQ(s), Fluticasone; Salmeterol(c)	400 mg	Insomnia, Vision blurred, Malaise	3	Yes	None/ Recovered
27	F/19	AS/AQ(s), Paracetamol(c)	200 mg twice daily	Dizziness, Vision blurred	2	Yes	None/ Recovered
28	M/28	AS/AQ(s)	812 mg once daily	Tongue disorder, Decreased appetite, Blindness transient	4	Yes	Unknown / Recovering

Table 1: *Characteristics of case reports of vision disorders associated with artesunate /amodiaquine in the WHO individual case safety reports database.*
F: Female; M: Male; AS/AQ: Artesunate/Amodiaquine.

AS/AQ was the only suspected drug in 21 of the cases, and was the sole drug administered in 11 cases. Time to onset was reported in all cases and median onset was found to be two days (range: 1 - 9) following initiation of AS/AQ. Reaction outcome was reported as 're-

covered' in 18 cases, 'recovering' in three cases, 'not recovered' in four cases and 'unknown' in the rest of the cases. Following withdrawal of AS/AQ, reaction abated in six of the cases and recurred in one case after re-introduction of the suspected drug. This association showed an IC value of 0.49 for the combination of blurred vision and AS/AQ; while negative for the other forms of vision disorders.

Metoclopramide (7.1%), primaquine (7.1%), nifurtimox (3.5%), doxycycline (3.5%), and eflornithine (3.5%) were among the co-suspected drugs in some of the cases. Asthenia, dizziness, insomnia and decreased appetite were also some of the co-reported reactions in majority of the cases.

Results of causality assessment of the series of cases using Hill's criteria are provided in table 2.

	Criterion	Outcome
1.	Strength of association	IC value for blurred vision and AS/AQ was found to be positive (0.49) which is statistical signal; while other forms of vision disorders were negative.
2.	Consistency of the cases	Similar cases were reported from different African countries. The availability of case report of binocular disorder following concurrent use of AS/AQ and mefloquine [2] also provides consistency of the association. In our study, most of the cases manifested vision disorders from the first to the fourth day following the intake of AS/AQ.
3.	Specificity of the association	In 11 cases, vision disorders manifested solely after the intake of AS/AQ; making the association specific.
4.	Temporal relationship	All reactions manifested shortly after the intake of AS/AQ with a median time to reaction onset of two days. In five cases, vision disorders manifested on the next day following the sole intake of AS/AQ.
5.	Dose-response relationship	Experimental animal studies with high doses of amodiaquine revealed visual disturbances [13,14]. There are also published case reports that documented vision disorders following overdose and/or prolonged use of amodiaquine alone [3-5].
6.	Biological mechanism or plausibility	The exact mechanism of action is unknown but this might be explained by the fact that drugs of the same class affect the metabolism of retinal cells by binding to melanin in the retinal pigment epithelial which might create visual disturbances [15].
7.	Experimental evidence	Serial electro-oculograms of five patients with chronic discoid lupus erythematosis given amodiaquine 250mg for one month showed a significant drop in the electro-oculogram values within a month of starting treatment. The drop in the electro-oculogram values completely return to normal within two months of stopping amodiaquine [5]. Furthermore, in six of the cases of our study, reaction recovered following withdrawal of AS/AQ and in one case, reaction recurred after reintroduction of the drug.
8.	Analogy	Hydroxychloroquine is a 4-aminoquinoline drug similar to amodiaquine in structure and activity and is known to cause retinal toxicity [15].
9.	Coherence	Amodiaquine at prolonged use and overdose has been associated with vision disorders [3-5] and AS/AQ has also been associated with the same adverse reaction in a published case report from Ghana [2]; both show coherence of the association.

Table 2: *Results of causality assessment between AS/AQ and vision disorders using Hill's Criteria.*
IC: Information Component; AS/AQ: Artesunate/Amodiaquine.

Discussion

The positive IC value in the global database indicates that the association of blurred vision and AS/AQ is observed more than expected. The association was also found to be consistent as the cases of vision disorders were reported from various countries using AS/AQ with a

similar pattern in time to reaction onset. Manifestation of vision disturbances following the sole intake of AS/AQ in a substantial number of cases also supports specificity of the association.

The mechanism by which AS/AQ causes vision abnormality is not known. However, hydroxychloroquine (HCQ), which is a structural analog of amodiaquine, has been associated with retinal toxicity through accumulation in tissues with melanin content [16]. The deposition of HCQ in retinal pigment epithelium (RPE) for prolonged periods of time leads to a toxic effect on the RPE causing degenerative changes leading to photoreceptor degradation [17]. *In vitro* studies on cultured RPE cells suggest that HCQ alters RPE lysosome pH, resulting in higher levels of lipofuscin [18]. This lysosomal damage leads to disruption of RPE metabolism and RPE degeneration and finally to photoreceptor loss [19]. The resemblance in structure and chemical properties of amodiaquine with quinine [15] can also be another feature which can support the causation.

The reversibility of the reaction in majority of the cases (64.3%) following discontinuation and/or completion of AS/AQ also supports the causal relationship. Retinal whitening, a patchy opacification of the retina, has been associated with malarial retinopathy [20] which might be an alternative explanation for some of the cases. The manifestation of retinopathy however, was associated with complicated malaria which is not the case in our situation. The effect of possible co-existence of renal [21], hepatic [22] or other conditions on vision disorders are residual confounders since they cannot be ruled out due to the nature of the study.

In few of the cases, doxycycline, eflornithine, metoclopramide, nifurtimox, and primaquine were reported as 'co-suspected' drugs, which might have also contributions in explaining the adverse effect of interest. The fact that AS/AQ was the only drug taken, and singularly exhibited the outcome in almost 40% of the cases strengthens the association.

Over all, the positive IC value, the plausible temporal relationship, the consistency of the cases, specificity of the association, the positive dechallenge in several cases and rechallenge in one case, the positive dose-response relationship observed with amodiaquine and report of similar reactions with other drug analogs support a causal relationship between AS/AQ and vision disorders.

As the data was compiled based from spontaneous reports (passive surveillance), the cases were not confirmed. Besides, due to the nature of the study, risk cannot be quantified as the true denominator cannot be determined.

Conclusion

This case series assessment found a suggestive causal link between short duration therapeutic doses of AS/AQ and vision disorders. We therefore recommend healthcare professionals to closely monitor patients taking AS/AQ and they should advise them to seek immediate medical attention if they encounter vision abnormalities, including blurred vision, to prevent further complications. And further epidemiological study is required to corroborate this study.

Competing Interests

The authors declare that they have no competing interests.

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Availability of Data and Materials

The dataset used for this publication is not allowed to be available for readers as it compromises the data privacy policy of patients. Aggregate data however can be submitted in reasonable request.

Ethics Approval and Consent to Participate

Not applicable.

Consent for Publication

Not applicable.

Disclaimer

The association presented in this article is those of the authors, and do not represent the opinion of the WHO or the Uppsala Monitoring Centre, Sweden.

Authors' Contributions

The idea was conceived by MR and all authors played a key role on the analysis and interpretation of the results. YF drafted the manuscript and edited by the rest of the authors.

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