ORIGINAL RESEARCH ARTICLE

Drug Saf 2012; 35 (8): 667-675
0114-5916/12/0008-0667/$49.95/0

Artesunate- and Amodiaquine-Associated Extrapyramidal Reactions

A Series of 49 Cases in VigiBase™

John McEwen

Discipline of Pharmacy, University of Canberra, Canberra, ACT, Australia

Abstract

Background: Acute extrapyramidal reactions have been attributed to amodiaquine. They may be anticipated with the widely-used combination antimalarial artesunate with amodiaquine, but the association is very poorly documented.

Objective: The aim of the study was to identify individual case safety reports in the Uppsala Monitoring Centre's Vigibase™ database associating the use of the combination of artesunate and amodiaquine with extrapyramidal adverse reactions and to characterize the clinical features in those reports.

Methods: Reports of adverse reactions to the combination use of artesunate or dihydroartemisinin and amodiaquine entered into Vigibase™ up to 15 February 2011 were identified. Reports with a causality grading of 'Unlikely' and probable duplicates of reports were excluded. Reports that included at least one MedDRA® Preferred Term strongly suggestive of an extrapyramidal reaction were subject to further detailed analysis.

Results: Forty-three reports in adults and six reports in children were identified as associating the use of artesunate with amodiaquine, either as separate co-packaged or fixed-combination products, with extrapyramidal reactions. More than half (57%) of the adults had an onset of the reaction within 48 hours of starting treatment. Almost equal numbers of male and female adult patients were reported – 67% were aged between 14 and 30 years. The most commonly implicated daily dose was amodiaquine base 600 mg and artesunate 200 mg, but lower doses were implicated in some adult patients. Identification of very long delays in some reports reaching Vigibase™ was an unexpected observation.

Conclusions: This case series supports an association of the use of artesunate and amodiaquine as combination antimalarial therapy with acute extrapyramidal reactions. The reactions occurred with recommended, and in some instances reduced, daily doses. Extrapyramidal reactions are unpleasant and frightening and the association warrants being more clearly recorded in official treatment guidelines and Summary of Product Characteristics documents.

Background

Acute extrapyramidal reactions have been associated with amodiaquine hydrochloride.[1-4] They may be anticipated with use of the combination of artesunate and amodiaquine hydrochloride, which is a treatment for uncomplicated falciparum malaria recommended by the WHO.[5] The association is, however, poorly documented. The purpose of the present study was to identify and analyse individual case safety reports (ICSRs) of extrapyramidal reactions during treatment with the combination of artesunate and amodiaquine submitted to the WHO Collaborating Centre for International Drug Monitoring, Uppsala, Sweden.

Methodology

The WHO Collaborating Centre in Uppsala is also known as the Uppsala Monitoring Centre (UMC). Data elements extracted from case reports received at national pharmacovigilance centres are submitted electronically to the UMC and held in a database (VigiBase™). The data elements in VigiBase™ are based on the CIOMS form 1a.[6] Searches of VigiBase™ were made on 15 February 2011 for reports in four categories: (i) with artesunate or amodiaquine nominated as a suspected medication and the other substance separately recorded as a suspected medication or recorded as a concomitant medication; (ii) 'amodiaquine with artesunate' as a suspected drug; (iii) 'amodiaquine hydrochloride with artesunate' as a suspected drug; and (iv) 'amodiaquine with dihydroartemisinin' as a suspected drug. Reports were classified as referring to children (<14 years of age) or adults (14 years of age and older) and then sorted in order of date of the onset of the reaction. Reports with identical (± 1 day) onset dates and additional identical or very similar data elements, such as patient age and sex and dates of administration of the medicine, were regarded as likely duplicate submissions and removed from further analysis, unless the contrary was established with the reporting national centre. Reports with a causality grading of 'Unlikely' and a report that changed only the adverse reaction terms of a previously submitted report, thus excluding an extrapyramidal reaction, were also removed. Reports that included at least one reaction term strongly suggestive of an acute extrapyramidal reaction were then selected and subjected to a series of further analyses. A search of the reporting to VigiBase™ of extrapyramidal reactions associated with amodiaquine in the absence of artesunate was also undertaken.

An understanding of the analysis of dosing requires a knowledge of the possible expressions of the doses of artesunate and amodiaquine. Artesunate is used in fractions or multiples of 50 mg. Amodiaquine is used as the hydrochloride. Amodiaquine hydrochloride 200 mg contains 153.1 mg of amodiaquine base. Amodiaquine is generally used in fractions or multiples of 153 mg. The adult daily dose recommended for most products is artesunate 200 mg and amodiaquine base 612 mg (153 × 4), although frequently expressed as 600 mg. In most reports where the suspected medicine was recorded in VigiBase™ as 'amodiaquine with artesunate', the adult daily dose has been stated as 800 mg, being the sum of the artesunate and amodiaquine doses (or an equivalent expression – 600 mg/200 mg; 612 mg/200 mg; 812 mg). The situation is further complicated by the trade names of some products including '1000', being the sum of the artesunate (200 mg) and amodiaquine hydrochloride (200 mg × 4) doses (1000 mg).

Results

Overall, 272 reports submitted prior to 15 February 2011 had a suspected drug in one of the four categories. All had a medication start date or a reaction onset date after 1 March 2005. Overall, 21 likely duplicates, 18 'Unlikely' reports (none with reaction terms suggestive of an extrapyramidal reaction) and the report modifying the earlier report were excluded from the series, leaving 232 reports about 199 adults and 33 children. They had been submitted from eight African countries – Burkina Faso, Cote d'Ivoire, Democratic Republic of the Congo, Ghana, Madagascar, Nigeria, Sierra Leone and Senegal. A wide variation in the time between onset date of the reaction and the date of entry into VigiBase™ was noted (figure 1).

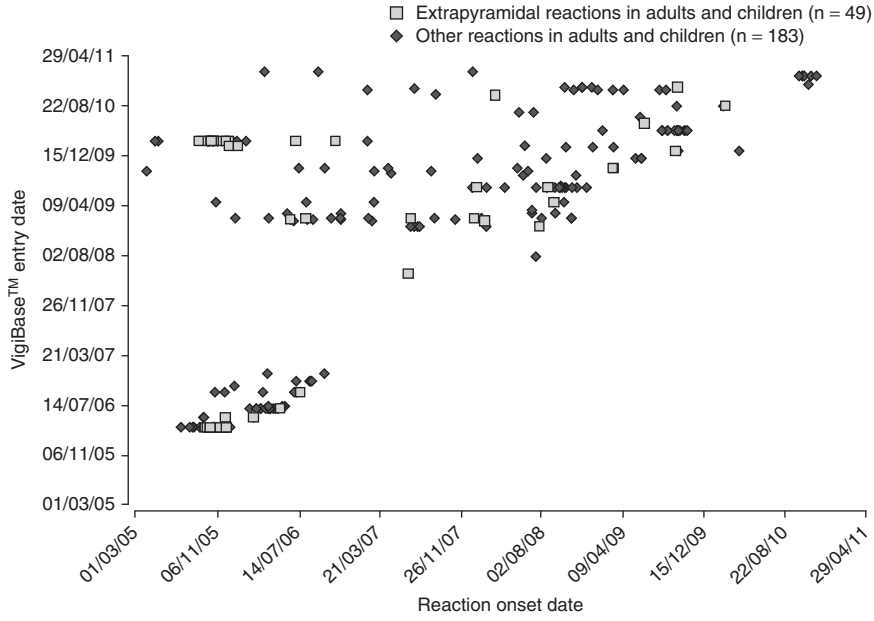

Fig. 1. Relationship between onset date and VigiBase™ entry date.

Of the most commonly mentioned MedDRA® Preferred Terms in the 232 reports,[7] 'Restlessness' (which includes the Lower-Level Terms 'Restlessness marked' and 'Restlessness aggravated'), with mentions in 24 reports, ranked equal fourth with 'Pruritus', after 'Asthenia' [includes weakness generalized] (77 mentions), 'Dizziness' (54) and 'Vomiting' (32). 'Dystonia' ranked seventh, with 18 mentions.

Adults

A total of 43 of the 199 adult reports included at least one MedDRA® Preferred Term consistent with an acute extrapyramidal reaction. Expanded details about each of these cases is available in the online Supplemental Digital Content (see table S1, http://links.adisonline.com/DSZ/A71). A further seven reports in adults with Preferred Terms describing an acute event involving movement disturbances other than convulsions, but not necessarily describing an extrapyramidal reaction, were also identified but not analysed further (table I). The 43 reports were from Ghana (n = 37), Nigeria (5) and Burkina Faso (1). None involved amodiaquine with dihydroartemisinin. The age and sex of 42 adult subjects are shown in figure 2; 67% were aged less than 31 years. The age of one adult subject was not stated.

The daily dose taken was described as 800 mg (or an equivalent expression – see Methodology section) in 24 reports. Nine different trade names of combination products associated with 800 mg/day were mentioned. It is believed that all except two were co-packaged ('co-blistered') presentations of separate tablets of artesunate and amodiaquine. Three reports implicated Artesunate-Amodiaquine Winthrop®, which has a daily dose of 540 mg of amodiaquine base. Three reports from Ghana, in subjects aged between 15 and 41 years, had a daily dose of 400 mg; three other reports from Ghana with therapy start dates after 1 January 2007 had a dose of 400 mg (expressed as 300 mg/100 mg in two) twice daily. Daily doses of 700 mg and 1140 mg were each mentioned once. The dose was not stated in eight reports. Concomitant medications were recorded in only seven reports. Multivitamin or folic acid products and paracetamol (acetaminophen) were each mentioned three times, and trimethoprim

with sulfamethoxazole, diclofenac, chloramphenicol and oral replacement solution were each mentioned once.

The latencies of onset of the reaction in 42 subjects (one report did not include a therapy start date) are shown in figure 3. Overall, 57% had an onset within 48 hours of starting the medicine. Four of the reports with an onset date on the fourth day (therapy start date day plus 3 days) had their onset date 1 day after therapy was stopped. For all other reports, the onset date was the same as, or earlier than, the date therapy was stopped, indicating that the combination product was probably being taken when the adverse event occurred.

Explicit information about or gradings of severity were included in only eight reports. In four of these the subject had been admitted to hospital. One subject (a 56-year-old woman with generalized weakness, dystonia and marked restlessness) died. The report stated that ''reaction may be contributory''. The outcomes in the other 42 reports were 'Recovered' or 'Recovering' (n = 22), 'Not stated' or 'Unknown' (n = 14) and 'Recovered with sequelae' (n = 6). In no case were the sequelae described. Causality assessments were recorded in only 12 of the 43 reports. They were Probable (n = 6), Possible (n = 4) and Certain (n = 2). Eleven of the 12 were submitted from Ghana, where causality had been assessed by expert opinion. Dystonia as the adverse event was overrepresented in these reports (8 of 11) compared with all reports from Ghana (14 of 37). Why this was so is not known. No other differences between reports with and without causality assessments were apparent.

Nineteen of the 43 reports had additional information in a narrative section. The narrative of one of the two 'Certain' reports stated that the subject ''had a similar reaction on taking artesunate/amodiaquine course in the past''. Another subject was said to have taken artesunate previously without an adverse effect. Two reports indicated that in each case one medication (e.g. amodiaquine) had been taken in the morning and the other in the evening. Neither report included sufficient temporal detail to unequivocally implicate amodiaquine. Five of the narratives described treatments given for the reaction – they involved at least two medications in each case. They included diazepam (four reports), promethazine hydrochloride parenteral (two), benzhexol (two), benztropine, intravenous fluids, intravenous hydrocortisone, Astymin® capsules (nutritional supplement) and chlorphenamine maleate (one report for each). The reporters to the pharmacovigilance centres were pharmacists, 19 reports; physicians, 8; other health professionals, 9; con-

Table I. Extrapyramidal reaction reports (adults)[a]

Included in analysis (n = 43)	Excluded from analysis [see text] (n = 7)
Restlessness (19)[b,c]	Slurred speech and twitching (1)[b]
Dystonia (15)[b]	Spasm (1)
Dystonia and facial spasm (1)	Spasms (1)
Restlessness marked and dystonia[b] (2)	Clonic spasm (1)
Torticollis (1)	Myoclonus (1)
Muscle tremor, neck stiffness and speech disorder (1)[b]	Speech disorder (1)
Movement disorder (1)[b]	Globus hystericus, eyes rolling and agitation (1)
Dyskinesia acute, twitching and hypersalivation (1)	
Tongue protrusion spastic involuntary and hypersalivation (1)	
Tongue protrusion spastic involuntary, muscle rigidity and hypersalivation (1)[b]	

a Further details of the cases are available in the online supplementary material (http://links.adisonline.com/DSZ/A71).

b Indicates that other MedDRA® Preferred Terms were also mentioned in some reports.

c The Lower-Level Terms 'Restlessness marked' (15 reports) and 'Restlessness aggravated' (4 reports) have been grouped under the Preferred Term 'Restlessness'.

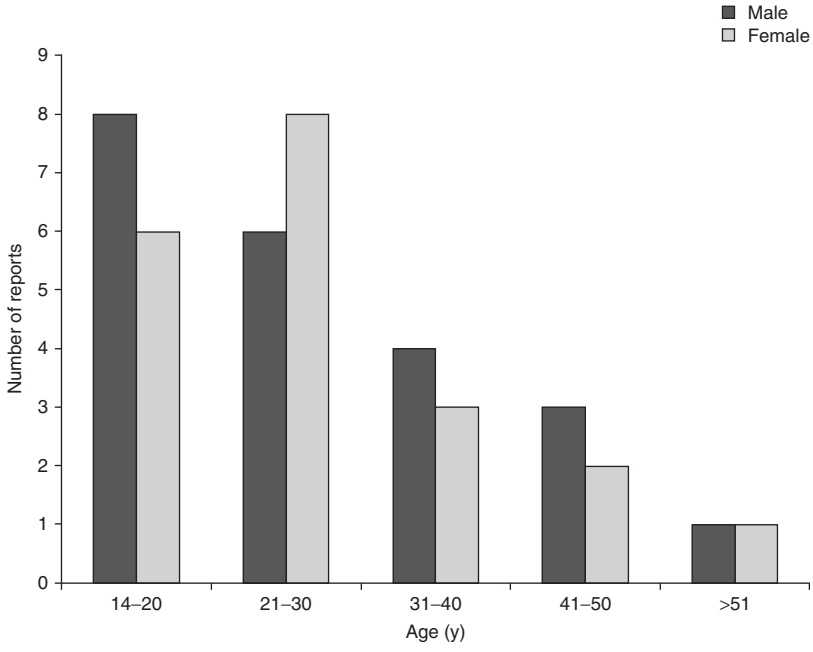

Fig. 2. Age and sex of adults with an extrapyramidal reaction (n = 42; one subject was specified as an adult but age was not stated).

sumer/non-health professionals, 5; and not stated in two reports.

Between March 1988 and 15 February 2011, 11 reports of extrapyramidal reactions in adults associated with amodiaquine in the absence of use of artesunate were entered into VigiBase™. In 9 of the 11 reports, amodiaquine was the sole suspected drug.

The 11 reports included dystonia (five reports), dyskinesia (one report) and tardive dyskinesia (two reports). The use of the term tardive dyskinesia may be questioned, as in neither case was amodiaquine nor the other suspected drugs taken for more than 4 days before the onset of the reaction. Judged by age and sex of the patient and onset date, none of these reports appear to duplicate published reports.

Children

There were six reports of extrapyramidal reactions, submitted from Senegal, Ghana (two reports each), Sierra Leone and Nigeria (one report each) [table II]. In one report, intramuscular metoprimazine, given for nausea and vomiting, was recorded as a suspected drug in addition to artesunate with amodiaquine. Between August 2005 and 15 February 2011, five reports of extrapyramidal reactions in children aged from 1 year to 13 years associated with amodiaquine in the absence of the use of artesunate were entered into VigiBase™. In all five reports, amodiaquine was the only suspected cause. Judged by age and sex of the patient and onset date, none of these reports appear to duplicate published reports.

Discussion

Case Series

Although the combination of artesunate and amodiaquine is an effective treatment for uncomplicated falciparum malaria, its acceptance has been claimed to be suboptimal because of community awareness of unpleasant adverse effects.[8] Acute extrapyramidal reactions to amodiaquine were first documented in 1976. Other reports have followed, but a report of an acute extrapyramidal reaction in a child is the only published report implicating the combination of

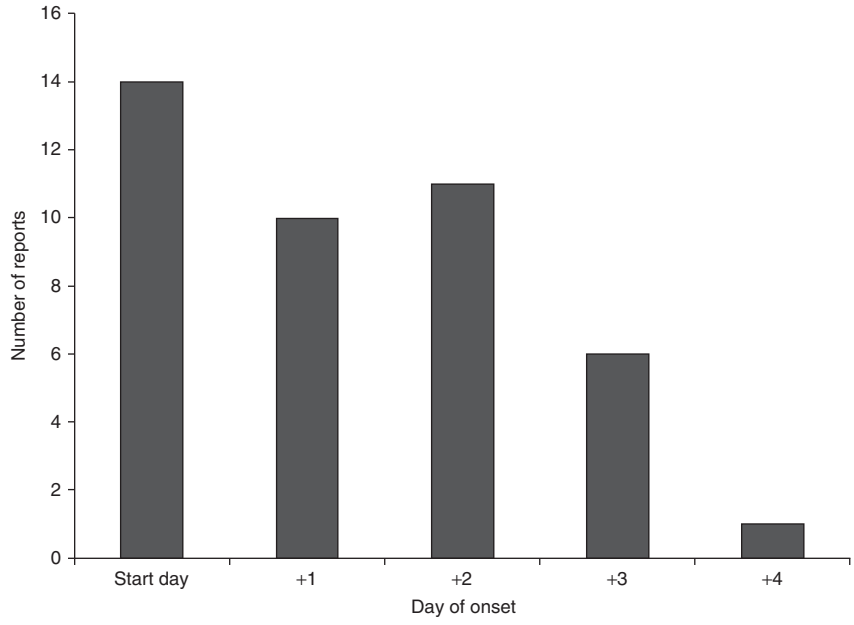

Fig. 3. Latency of onset of extrapyramidal reactions (n = 42; one report did not include a therapy start date).

artesunate and amodiaquine.[9] Acute dystonia and acute dyskinesia are characteristic of an extrapyramidal reaction. Restlessness (akathisia) may also be caused by medicines.[10] Taken together with a smaller number of reports of other symptoms, the series of cases in VigiBase™ reported here supports an association with the combination. Given that extrapyramidal reactions have been associated with amodiaquine monotherapy, it is the likely causal agent. The reported reactions occurred mainly in younger adults (<31 years of age) and there was no obvious difference between the sexes, unlike that which has been reported with metoclopramide.[11] Although recorded in only a few cases, most of the treatments given were as would be used in other parts of the world to treat acute extrapyramidal reactions and the majority of subjects recovered at the time of reporting. In no case was metoclopramide cited as a concomitant medication or treatment,

Table II. Reports of extrapyramidal reactions in children (n = 6)

Number	Preferred Terms	Age and sex	Daily dose	Latency of onset	Outcome
1	Dystonia	'Child' (F)	Not stated	Start day	Not stated
2	Extrapyramidal disorder	3 years (M)	Not stated[a]	Start day	Recovered
3	Extrapyramidal disorder	12 years (F)	Not stated	Next day	Recovered
4	Restlessness marked, nausea, weakness generalized, dyspnoea	2.5 months (M)	203 mg oral	Next day	Recovered
5	Restlessness marked, weakness generalized	3 years (M)	300 mg oral	Next day	Recovered
6	Restlessness marked, shivers, tongue protrusion spastic involuntary	8 years (F)	Amodiaquine 200 mg; artesunate not stated	Two days after start	Recovered

a Metopimazine also reported as a suspected cause.

F = female; **M** = male.

diminishing the chance that these events were a reaction to a treatment for nausea caused by the antimalarial therapy. Use of a phenothiazine was recorded only in two adult reports and one child report. There were no reports of concomitant use of efavirenz or other medicines that might alter the metabolism of amodiaquine by the cytochrome P450 2C8 isoenzyme.[12] The reports do not illuminate the possible influence of pharmacogenetic characteristics in these subjects.[13]

In this case series, the most commonly implicated daily dose was artesunate 200 mg and amodiaquine 600 mg. Lower doses have been implicated, including the use of artesunate 100 mg with amodiaquine 300 mg once or twice daily. Twice-daily dosing with artesunate 100 mg and amodiaquine 300 mg was recommended in Ghana in early 2006 in an attempt to reduce the incidence of adverse effects of the combination.

The initial and current guidelines for the treatment of malaria state that ''large doses of amodiaquine have been reported to cause syncope, spasticity, convulsions and involuntary movements''.[14,15] The reference to 'large doses' is potentially confusing as it follows a sentence about 'overdose toxicity' and because the daily dose of amodiaquine taken by adults mentioned in the published case reports (600 mg) is a recommended daily dose. Since 2007, bi-layered tablets containing both artesunate and amodiaquine in a single tablet (Artesunate Amodiaquine Winthrop®) have been available. The tablet intended for adult dosing contains artesunate 100 mg and amodiaquine base 270 mg. Two tablets (i.e. 200 mg artesunate and 540 mg amodiaquine base) are to be taken once daily for 3 days. The reduction of 60 mg in the adult daily dose of amodiaquine base reflects use of weight-for-age reference data for designing age-based dosing regimens.[16] No study has been conducted capable of demonstrating the superiority of the 540 mg dose over the 600 mg dose with respect to less common adverse reactions.

There is a general lack of standardization in recording and reporting of adverse events in clinical studies of artemisinin-containing combination treatments.[17,18] The majority of subjects in studies of artesunate with amodiaquine have been children, which would be of importance if appropriate studies were to demonstrate higher rates of these reactions in adults compared with children.

Concerning neurological adverse effects, the Summary of Product Characteristics (SPC) for Artesunate Amodiaquine Winthrop® refers to somnolence, paraesthesias, headache, dizziness, convulsion and rare neuromyopathy.[19] There is no mention of movement disorders, extrapyramidal disorders or their common pathognomonic symptoms, which is curious as the SPC purports to include additional types of events that have been attributed to amodiaquine in the published literature. In a recent application for inclusion of the product in the Essential Medicine List, the sponsor stated, four times, that the fixed-dose combination was formulated to ensure that patients take both drugs together ''in the right dose''.[20] The three reports in VigiBase™ implicating Artesunate Amodiaquine Winthrop® as the cause of extrapyramidal reactions suggest that the dose difference may be clinically unimportant and that the addition of this association to the SPC should be considered. Addition to the SPC for amodiaquine (150 mg base) tablets (Guilin Pharmaceutical Co. Ltd, Guangxi, China) should also be considered, as it has an identical description of neurological adverse effects.[21]

Data made available by the UMC must be accompanied by a statement of certain caveats.[22] These include that the information is not homogeneous at least with respect to origin or likelihood that the pharmaceutical product caused the adverse reaction, and that the information does not represent the opinion of the WHO. Because exposure to the combination is not known and there may be significant underreporting, it is not appropriate to use these reports to the UMC to estimate the incidence. Exposure to the combination is very large (in 2005, 13.9 million treatment courses of artesunate and amodiaquine were ordered through the WHO)[23] and the incidence of extrapyramidal reactions may be rare (<1/1000 exposures to ≥1/10 000) or very rare (<1/10 000). Even if very rare, the very high exposure will result in a substantial number of these reactions each year.

Delays in Report Submission

Concern has been expressed about the difficulties of conducting pharmacovigilance in Africa.[24] This study has found that there have been very considerable delays in the submission from national pharmacovigilance centres in Africa to the UMC of some ICSRs describing adverse reactions to the artesunate and amodiaquine combination. The delays may be a reflection of limited resources devoted to national pharmacovigilance in Africa and difficulties in accessing adequate Internet connections for the transmission of reports to UMC. There has, however, been some improvement recently (figure 1).

Conclusions

Acute extrapyramidal reactions are often frightening and unpleasant for a patient, but are readily treated. Notwithstanding the limitations in available information inherent in analyses of UMC case records and the observed delays in reporting to the UMC, contributions from national centres in Africa have allowed the identification of a series of cases of extrapyramidal reactions associated with the use of the combination of artesunate with amodiaquine. It is important that the association is known to all who prescribe and distribute these combination products.

Acknowledgements

Marie Lindquist (Director, UMC), Ralph Edwards (Former Director, UMC) and Alex Dodoo (Director, WHO Collaborating Centre for Advocacy and Training in Pharmacovigilance, Accra, Ghana) encouraged the author to undertake the review. The WHO Collaborating Centre for International Drug Monitoring has authorized the use and publication of the VigiBase™ data. Alex Dodoo and Mimi Darko (Food and Drugs Board, Ghana) readily answered many questions. Richard Hill and Sara Hult (UMC) assisted greatly with searches of Vigibase, and Monica Ploen resolved some data retrieval difficulties identified during the study. The author presented key data from this paper in the Bengt-Erik Wiholm Memorial Lecture, 11th Annual Meeting, International Society of Pharmacovigilance, Istanbul, Turkey, 27 October 2011.

There was no funding for the study. John McEwen proposed the study, undertook the searches of VigiBase™, analysed the data and prepared the report. He undertook the study in his free time. He certifies that he has had full access to all the data in the study and decided to submit the paper for publication.

John McEwen is a volunteer (unpaid) member of a panel of reviewers of data for the UMC. He had a short-term contract with the WHO in 2006 to provide an expert review of reports of suspected reactions to artesunate with amodiaquine in Ghana. He is an (unpaid) Adjunct Associate Professor, Discipline of Pharmacy, University of Canberra, Canberra, ACT, Australia. He is a part-time Medical Adviser, Therapeutic Goods Administration, Australia, contracted until May 2013, and has undertaken paid evaluations of medicines for the Australian Department of Health and Ageing. He has, in the past 4 years, undertaken paid expert evaluations for the WHO of vaccines proposed for pre-qualification. He has had travel expenses reimbursed, accommodation reimbursed and in some instances been paid a per diem fee or a gratuity to give pharmacovigilance training for the International Society of Pharmacovigilance, the Chinese University of Hong Kong, Health Sciences Authority Singapore, IBC Asia (S) Pte Ltd and the Government of Indonesia, and to review pharmacovigilance arrangements for the Governments of Hong Kong and Vanuatu. In 2010, at the request of the WHO, he gave unpaid advice about pharmacovigilance of an antimalarial drug (not artesunate with amodiaquine) to the European Medicines Agency.

References

1. Akindele MO, Odejide AO. Amodiaquine-induced involuntary movements. BMJ 1976; 2: 14-5
2. Adonis-Koffy L, Daubrey T, Kouadio A, et al. Effets neurologiques indésirables méconnus de l'amodiaquine. Bull Soc Pathol Exot 2003; 96: 302-7
3. Kamagaté M, Dié-Kacou H, Balayssac E, et al. Oro-facial dyskinesias and amodiaquine [letter]. Therapie 2004; 59: 565-6
4. Akpalu AK, Nyame PK, Dodoo ANO. Amodiaquine-induced dystonic reactions: case reports and implications for policy change in Ghana. Int J Risk Safety Medicine 2005; 17: 1-4
5. World Health Organization. Guidelines for the treatment of malaria. 2nd ed. Geneva: World Health Organization, 2010: ix
6. Lindquist M. VigiBase, the WHO global ICSR database system: basic facts. Drug Inf J 2008; 42: 409-19
7. Introductory guide to standardised MedDRA queries (SMQs). Version 14.0. Chantilly (VA). Maintenance and Support Services Organization, 2011 Mar
8. Dodoo ANO. Global support for regional problems? Uppsala Reports 2008; 43: 13 [online]. Available from URL: http://www.who-umc.org/graphics/24357.pdf [Accessed 2010 Jun 16]
9. Fajolu IB, Lesi FEA. Drug-induced acute dystonia in a 7 year old child following the use of artesunate-amodiaquine: a case report. Int J Risk Saf Med 2010; 22: 111-4
10. Ball R. Drug-induced akathisia: a review. J R Soc Med 1985; 78: 748-52
11. Bateman DN, Rawlins MD, Simpson JM. Extrapyramidal reactions with metoclopramide. BMJ 1985; 291: 930-2
12. Parikh S, Ouedraogo JB, Goldstein JA, et al. Amodiaquine metabolism is impaired by common polymorphisms in CYP2C8: implications for malaria treatment in Africa. Clin Pharmacol Ther 2007; 82: 197-203

13. Gil JP. Amodiaquine pharmacogenetics. Pharmacogenomics 2008; 9: 1385-90
14. World Health Organization. Guidelines for the treatment of malaria. Geneva: World Health Organization, 2006: 89
15. World Health Organization. Guidelines for the treatment of malaria. 2nd ed. Geneva: World Health Organization, 2010: 75
16. Taylor WRJ, Terlouw DJ, Olliaro PL, et al. Use of weight-for-age-data to optimize tablet strength and dosing regimens for a new fixed-dose artesunate-amodiaquine combination for treating falciparum malaria. Bull World Health Organ 2006; 84: 956-64
17. Staedke SG, Jagannathan P, Yeka A, et al. Monitoring antimalarial safety and tolerability in clinical trials: a case study from Uganda. Malar J 2008; 7: 107-17
18. Sinclair D, Zani B, Donegan S, et al. Artemisinin-based combination therapy for treating uncomplicated malaria. Cochrane Database Syst Rev 2009; (3): CD007483
19. Summary of product characteristics: artesunate/amodiaquine tablets (Sanofi-Aventis), MA056, MA057, MA058. In: WHOPAR part 4. 09/2010, version 1.1: 6-7 [online]. Available from URL: http://apps.who.int/prequal/WHOPAR/WHOPARPRODUCTS/MA058part4v1.pdf [Accessed 2011 May 30]
20. Sanofi-Aventis. Application for inclusion of artesunate/amodiaquine fixed dose combination tablets in the WHO model lists of essential medicines. June 2009, updated Sept 2010 [online]. Available from URL: http://www.who.int/selection_medicines/committees/expert/18/applications/Sanofi_application.pdf [Accessed 2011 Mar 28]
21. Summary of product characteristics: amodiaquine (150 mg base) tablets (Guilin), MA045. In: WHOPAR part 4. 06/2011 [online]. Available from URL: http://apps.who.int/prequal/WHOPAR/WHOPARPRODUCTS/MA045part4v2.pdf [Accessed 2011 Sept 15]
22. Caveat document: accompanying statement to data released from the WHO Collaborating Centre. WHO Collaborating Centre for International Drug Monitoring [online]. Available from URL: http://www.who-umc.org/graphics/25027.pdf [Accessed 2011 Jun 19]
23. WHO briefing on malaria treatment guidelines and artemisinin monotherapies. Geneva: World Health Organization, 2006: 17 [online]. Available from URL: http://www.who.int/malaria/publications/atoz/meeting_briefing19april.pdf [Accessed 2011 May 19]
24. Talisuna AO, Staedke SG, D'Alessandro U. Pharmacovigilance of antimalarial treatment in Africa: is it possible? Malar J 2006; 5: 50-8

Correspondence: Dr *John McEwen*, 253 La Perouse Street, Red Hill, ACT 2603 Australia.

