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Clinical picture and outcome of Serious Adverse Events in the treatment of Onchocerciasis

Kwablah Awadzi*

Address: Onchocerciasis Chemotherapy Research Centre (OCRC) Hohoe Hospital, Hohoe, Ghana

Email: Kwablah Awadzi* - awadzi@ghana.com

* Corresponding author

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Abstract

Ivermectin (Mectizan®) is the only drug currently recommended for the treatment and control of onchocerciasis. Serious adverse events rarely occur during treatment, except in subjects heavily infected with Loa Loa. This review of drug-related serious adverse events in the treatment of onchocerciasis therefore revisited the pre-Mectizan® reference drugs, DEC and suramin, and other candidate drugs studied extensively for the treatment of human onchocerciasis. The benzimidazole carbamate derivatives and the antibiotic doxycycline were excluded, since no serious adverse events have been reported regarding their use. Using recommended definitions, serious adverse events reported or observed after the use of each drug were summarised, the level of attribution determined, and the results tabulated. Prominence was given to treatment-related deaths. The clinical picture of severe symptomatic postural hypotension is described and used to illustrate the difference between the severity and the seriousness of an adverse event. The epidemiology, management and outcome of serious adverse events are presented. The role of future research is discussed.

Introduction

The efforts made through more than four decades of research yielded ivermectin (Mectizan®) as the only drug to be recommended for the treatment and control of onchocerciasis. The activity against the microfilariae (mf) of *Onchocerca volvulus* in a single dose of 150–200 μg/kg [1], and against the adult worms on repeated dosage [2–6], testifies to the efficacy of the drug. The distribution, monitoring and management of adverse events in the community by individuals with little medical knowledge are proof that Mectizan® rarely produces Serious Adverse Events (SAEs) in the onchocerciasis patient. Hence, this contribution to the clinical spectrum of drug-related serious adverse events in the treatment of onchocerciasis also examines the pre-Mectizan® "reference" drugs, diethylcarbamazine (DEC) and suramin, and other drugs studied extensively for the treatment of human onchocerciasis. The drugs and their effects against *O. volvulus* are listed and summarised in Table 1. There have been no SAEs attributed to mebendazole [7,8], flubendazole [9] albendazole [10–12] or doxycycline [13]. They will therefore not be considered further. In addition, little reference will be made to melarsonyl potassium (not listed) – a potent macrofilaricide that resulted in death from arsenical encephalopathy [14,15].

Definitions

Serious Adverse Event (SAE)

As defined in the International Conference on Harmonisation of Technical Requirements for Registration of Phar-

Table 1: Drugs and their activity against *Onchocerca volvulus*

Chemical group	Effect on *O. volvulus*			
	Microfilariae	Adult worms		
	Lethal effect	Lethal effect	Embryo-Toxicity/depletion	Embryo-sequestration*
Avermectin				
Mectizan®	++++	0 to ++**	0 to ++**	++++
Urea derivative				
Suramin	+++	++++	++++	0
Piperazine derivative				
Diethylcarbamazine	++++	0	0	0
Organophosphate				
Metrifonate	+++	0	0	0
Benzimidazole carbamate				
Mebendazole	++	0	++	0
Flubendazole	0	0	++	0
Albendazole	0	0	+++	0
Thiourea				
Amocarzine†	+++	0	0	0
Tetracycline				
Doxycycline‡	0	0	++++	0

* A block to the release of microfilariae is the primary effect, followed by their degeneration *in utero* ** On multiple dosage † Not registered ‡ Experimental drug

maceuticals for Human Use (ICH) Harmonised Tripartite Guideline for Good Clinical Practice [16], a serious adverse event is "any untoward medical occurrence that, at any dose a) results in death b) is life-threatening c) requires inpatient hospitalisation or prolongation of an existing hospitalisation d) results in persistent or significant disability/incapacity or e) is a congenital anomaly/ birth defect." A modification to these criteria [17] has included important medical events that may not be immediately life threatening, or result in death or hospitalisation, but that may jeopardize the patient, or require intervention to prevent the other outcomes listed above.

Causality or Attribution

When an adverse event is recorded, the relationship to the medicinal product (causality) needs to be determined, as this has important implications for the future use of the product. Various terms define this relationship. One such set of definitions [17] is as follows:

1) Not related: The experience is clearly related to other factors such as the patient's clinical state, therapeutic intervention or concomitant therapy.

2) Unlikely: The experience was most probably produced by other factors, such as the patient's clinical state, therapeutic intervention or concomitant therapy, and does not follow a known response pattern to the trial product.

3) Possible: The experience follows a reasonable temporal sequence from the time of product administration, *and/or* follows a known response pattern to the trial product, *but* could have been produced by other factors such as the patient's clinical state, therapeutic intervention or concomitant therapy.

4) Probable: The experience follows a reasonable temporal sequence from the time of product administration, *and/or* follows a known response pattern to the trial product, *and* could not have been produced by other factors such as the patient's clinical state, therapeutic intervention or concomitant therapy.

5) Most probable: The experience follows a reasonable temporal sequence from the time of product administration, *and/or* follows a known response pattern to the trial product, *and* could not have been produced by other factors such as the patient's clinical state, therapeutic intervention or concomitant therapy, *and* either occurs immediately following trial product administration, or improves on stopping the product, or there is positive reaction at the application site.

With the drugs under consideration, adverse events that resulted in death will be summarised, followed by other categories of SAEs and the determination and discussion

of causality. Although they are described under separate systems, adverse events tend to be multi-systemic.

SAEs associated with various drugs

Deaths

The administration of a total dose of 10 g of suramin over a period of 19 days to 20 patients resulted in four deaths [18]. Doses in excess of 6.0 g have also resulted in death [19–21]. These were due to over-dosage. However, the deaths of two patients who were treated with what would be currently acceptable doses [22] were also probably due to drug effects. In both cases, the patients complained of oropharyngeal pain, refused to eat or drink and had prolonged diarrhoea; there was no response to corticosteroid therapy. Reports of death in 11% of 592 treated patients, occurring six years after completion of a total dose of 10 g of suramin, [23] and after four years in 6% and 18% of patients in two hyper-endemic villages treated with a total dose of 4–6 g of suramin [22] were possibly related to therapy. Death also occurred in 7 out of 327 patients treated with DEC [24]. All the patients were in poor general health, were malnourished, and had underlying chronic medical conditions. They all lapsed into a coma after taking 225 – 900 mg of the drug over 3 to 8 days, and died 1 to 4 days after the onset of the coma. There was no classical Mazzotti reaction and they failed to respond to supportive therapy and corticosteroids. A young man given low dose DEC under betamethasone cover [25] died on the third day in a state of shock and respiratory distress. His liver and spleen were moderately enlarged prior to treatment. In these DEC-related deaths, it is unlikely that the drug was the cause. The event was most probably produced by other factors, such as the patient's clinical state, other therapeutic intervention or concomitant therapy, and did not follow the known response pattern to DEC. Similarly, the death of an elderly woman from chicken pox two weeks after completing a DEC plus betamethasone course [25] was unlikely to be due to DEC.

Syndromes of collapse and "therapeutic shock"

This brings together accounts of life threatening clinical situations that followed treatment with DEC. They were associated with prostration, syncope, collapse and hypotension [26–28]. The term "therapeutic shock" was coined to describe the clinical status of the patient [29]. These were desperately ill patients with multi-system involvement.

A related but distinct adverse effect is severe symptomatic postural hypotension (SSPH). In the classical case, the pulse and blood pressure are normal while recumbent. On standing for a short while (a few minutes), there is dizziness, weakness or faintness and the patient becomes restless or confused; occasionally syncope occurs. The pulse rate increases in successive recordings, gets fainter and becomes impalpable, whilst blood pressure falls in a similar fashion. On assuming the recumbent position, bradycardia, drowsiness and diaphoresis occur. [30]. Usually, recovery follows rapidly and no treatment is necessary. SSPH has been described after treatment with virtually all microfilaricides except mebendazole [30–33]. It is one of the few adverse events that occurred to the same extent when equipotent doses of DEC and Mectizan® were given to patients with similar intensities of infection with *O. volvulus* [34]. SSPH is, par excellence, a "severe" adverse event that is usually not "serious" since it is so readily and simply reversible. During the field trials of Mectizan® conducted by the Onchocerciasis Control Programme (OCP) http://www.who.int/ocp/, several cases of SSPH were recorded in the early stages. The incidence fell dramatically when patients who felt weak or dizzy were asked to remain recumbent and send for the nurse rather than walk to the monitoring station [35]. However, in a few subjects, multiple episodes occur in quick succession. Under these circumstances, intervention that is more specific is required, in order not to jeopardize the patient. It is only then that SSPH becomes an SAE. Two patients who suffered "severe sustained postural hypotension" after Mectizan® [36] fall into this category.

Idiosyncratic reactions

Rarely, collapse with nausea, vomiting, shock, sweating and loss of consciousness have followed the initial injection of suramin [37]. As a precaution, a test dose of 100–200 mg (1 to 2 ml of a 10% solution) injected slowly over 3 minutes was advocated [38].

Dermatology/Skin

Adverse skin reactions to microfilaricides rarely justify hospitalisation, except where extensive secondary infection has followed prolonged scratching. An exception occurs when patients with hyper-reactive onchodermatitis are treated with any microfilaricide. This may result in severe, prolonged itching, an extensive oedema of the skin, and limb swelling. In one report, repeated intravenous corticosteroid injections over 3 days were required to control symptoms [39]. Exfoliative dermatitis is an uncommon late manifestation of suramin therapy [22,40]. A patient treated with suramin in northern Ghana developed exfoliative dermatitis and the palms of the hands and the soles of the feet came off as complete casts ("suramin casts"; Awadzi, unpublished observation).

Lymphatic

Extensive swelling of lymph glands, commonly in the groins, with oedema of the overlying skin extending over the pubis and lower abdomen occurs in heavily infected patients treated with DEC or metrifonate and, rarely, with Mectizan®. Pain is often severe and patients are unable to

turn over in bed due to reflex flexion of the hips. At best, they assume the "knee elbow position". They also become rooted to the spot when asked to walk – the "pillar of salt effect" [41].

Gastrointestinal

The administration of metrifonate daily for three or more days resulted in very severe abdominal colic due to the muscarinic effects of accumulated acetylcholine. In one study, abdominal pain occurred in 20 out of 34 patients and was unaffected by belladonna alkaloids started orally two days before and continued for a week. The pain persisted for several days after the completion of treatment [42].

Ulceration of the gastrointestinal tract rarely occurs with suramin. Stomatitis was observed in 1 of 100 patients treated [22]. Much more extensive ulceration was observed in one patient treated in northern Ghana (Awadzi, unpublished observation). Chronic diarrhoea was always an ominous sign of suramin toxicity. A histopathological examination of a chimpanzee after treatment with the equivalent of a 9 g dose of suramin for humans showed the intestines to be the organ most severely affected [43]. These gastrointestinal manifestations were probably due to over-dosage.

Pulmonary

During the OCP Mectizan® trials, in which more than 50,000 persons were treated, life threatening dyspnoea occurred in three patients within 24 hours of treatment [35]. Two were known asthmatics. The author was present during these attacks. One, a young male adult, had experienced asthmatic attacks previously but these had always responded to paracetamol; the post-Mectizan® attack did not. The other, a young adult female had attacks usually at the time of the full moon. Her attack occurred when the moon was full but was much more severe than previously. Multiple episodes occurred and she required intravenous aminophylline injections plus betamethasone therapy. Multiple attacks also occurred in a known asthmatic during the hospital-based trials (Awadzi, unpublished observation). These episodes were possibly related to Mectizan® therapy. The third patient with dyspnoea was a young adolescent male who had laryngeal oedema following an upper respiratory tract infection. His attack was not related to Mectizan® therapy. Recurrent bronchospasm requiring adrenaline therapy occurred 6 hours after treatment with metrifonate in a patient with no previous history [44]. Here also, the attack was possibly related to therapy.

Ulceration of the tracheobronchial tree is a rare manifestation of suramin toxicity. In one unpublished case from northern Ghana, expectoration of a "cast" of a bronchus composed of mucus and blood was observed. The same patient had produced casts of the soles and palms referred to above. He also had stomatitis and buccal ulceration. These manifestations resulted from over-dosage due to an error in the calculation of the total dose of suramin.

Musculoskeletal

A severely painful, acute polyarthritis involving mainly the knees, ankles, wrists, small joints of the fingers, and the elbows has been described following treatment with metrifonate and DEC. It began several days after the onset of therapy, when the peak of the initial reaction had passed, and hence was termed a "secondary reaction" [34,42]. Associated features were fever, sterile joint effusions with polymorphonuclear cells and microfilariae, and a raised erythrocyte sedimentation rate. Such adverse events have not been reported with Mectizan®. A similar syndrome with a sub-acute course occurred late during suramin therapy or during the post treatment observation phase. In addition, painful immobilisation of the hip joint in a semi-flexed position has been described. This was attributed to a reaction around dead worm bundles lying against the capsule of the joint [45].

Neurological

Cerebral toxicity occurred when the total dose of amocarzine given within 48 hours in the fasting state was 30 mg/kg or greater. When given after a meal, similar effects occurred at 25 mg/kg [46]. This involved 8 out of 39 patients (5/9 at 45 mg, 2/20 at 30 mg/kg and 1/10 at 25 mg/kg). There was mental confusion in all 8 patients. At 45 mg/kg, two patients performed repetitive extension movements of the neck, arms and legs while "searching movements" with the arms occurred in one markedly apathetic patient. Another patient was extremely aggressive and had to be restrained. Other features were inappropriate jocularity, perseveration, failure to concentrate, drowsiness and incontinence. The onset was 30 hours or more after drug administration, lasted from one to 47 hours and was followed by a complete recovery. These adverse events were attributed to the pharmacological properties of the drug.

Vertigo with prostration and incapacitation has been attributed to the mobilisation of microfilariae into the cerebrospinal fluid. The associated headache, nausea and vomiting may also have been of a central nervous system origin. A Parkinsonian-like syndrome lasting for seven days was also observed [47].

Marked proximal muscle weakness involving the neck, shoulder and pelvic girdles, with retention of distal muscle function, occurred after the fifth of a planned six daily dose regimen in one patient treated with metrifonate [42]. There was no sensory deficit. He was bedridden for 3 days.

The last dose was omitted. The event was attributed to the nicotinic effects of accumulated acetylcholine.

Constitutional symptoms and other systemic features

Fever, fatigue, general weakness and, rarely, prostration of short duration occur after treatment with microfilaricides. However, with suramin therapy they may be prolonged and herald a grave prognosis. The occurrence of jaundice with amocarzine [46] and suramin therapy [48] was unlikely to be due to drug therapy. Despite the frequency of proteinuria with suramin therapy, no renal associated SAEs have been documented.

Ocular/Visual

Anterior segment inflammation, with iridocyclitis, posterior synechiae and secondary glaucoma, and involvement of the posterior segment with optic neuritis, optic atrophy and visual field defects, have occurred following treatment with DEC and suramin. Lesions of the posterior segment occurred early with DEC treatment [49]. Fluorescein angiography demonstrated leakage of dye from the optic disc and disturbances of the retinal pigment epithelium before ophthalmoscopic changes were apparent [50]. Anterior segment lesions due to suramin did not occur for several weeks and optic atrophy developed after several months [51,52].

Epidemiology of drug-related SAEs in the treatment of onchocerciasis

Adverse effects occurring during the treatment of onchocerciasis may be due to:

1) The intrinsic properties of the drug

2) Therapeutic misadventure

3) The effect on the parasite-microfilariae (death-mobilisation into body fluids), and rarely to the death of the adult worms

4) A progressive disability from pre-existing lesions

5) A coincidental illness occurring in temporal relationship with drug administration or

6) Other factors.

With suramin, metrifonate and amocarzine, intrinsic drug effects are combined with parasite factors in the generation of the adverse events.

Intrinsic properties of the drug

Adverse events may be an expression of the pharmacological properties of the drug. They may have little to do with efficacy against the parasite. The event could be a manifestation of over-dosage either due to pure guesswork in the selection of the dose regimen, as occurred in the early days of suramin therapy [18], to an error in dispensing or administration, as occurred with the Ghanaian patient mentioned above, or to a direct extrapolation of data from animal experiments. In the cattle *O. gibsoni* model, amocarzine was macrofilaricidal at a dose of 40 mg/kg given daily for 3 days [53]. The equivalent dose in man would be 2000 – 2400 mg given daily for 3 days (total 6000 – 7200 mg). Single doses up to 1600 mg were shown to be safe in the fasting state. However, when 1200 mg were given daily for 2 days (total 2400 mg), severe cerebrotoxicity occurred in 5/9 patients, without any manifestation of a macrofilaricidal effect [46]. On the other hand, SAEs could follow an inexplicable pattern, as occurred during the use of melarsonyl potassium [14,15]

Therapeutic misadventure

Several factors need to be considered in the treatment of any disease, especially if the outcome is not fatal. Here, the application of basic therapeutic principles must predominate over the urge to treat. The health care provider must decide:

1) Whether the patient should be interfered with

2) What alteration in the patient's status one hopes to achieve

3) What other effects the drug may have and whether these would be harmful

4) Whether the likelihood of benefit outweighs the likelihood of damage.

The general medical status of the patient and the presence of coexisting medical conditions greatly influence the outcome of therapy, especially with drugs such as suramin [38]. Some fatalities in the treatment of onchocerciasis may have been due to a lack of consideration of these principles.

Parasite death

For a given dose of a microfilaricide, parasite related SAEs are more likely to occur in patients with high skin and ocular microfilarial loads [35,54]. The reduction in high microfilarial counts in skin predisposes to events that result in hospitalisation or prolongation of existing hospitalisation, while involvement of the ocular/visual system could result in persistent incapacity or disability. Additional factors are the concatenation of severe reactions involving multiple systems, such as occurred in patients with "therapeutic shock" and the coexistence of other filarial parasites, especially *L. loa* [55]. Gastrointestinal

Table 2: Onchocerciasis – SAEs, Drugs administered and the Level of Attribution

Category/Adverse event	Drug and Level of Attribution*				
	Mectizan®	DEC	Metrifonate	Suramin	Amocarzine
Death	1	2	1	4**	1
Syndromes of collapse					
"Therapeutic shock"	1	4	4	1	1
Recurrent SSPH	4	4	4	1	4
Idiosyncratic	1	1	1	4	1
Dermatology/Skin					
Hyper-reactive response	4	4	1	1	1
Exfoliative dermatitis	1	1	1	4	1
Lymphatic syndromes	4	4	4	1	4
Gastrointestinal					
Abdominal colic	1	1	4	1	1
GIT† ulceration	1	1	1	4	1
Chronic diarrhoea	1	1	1	4	1
Pulmonary					
Bronchospasm	3	1	3	1	1
Bronchial ulceration	1	1	1	4	1
Musculoskeletal					
Acute polyarthritis	1	4	4	1	1
Subacute polyarthritis	1	1	1	4	1
Hip immobilization	1	1	1	4	1
Neurological					
Cerebrotoxicity	1	1	1	1	4
Vertigo	1	3	1	1	1
Parkinsonian-like state	1	3	1	1	1
Proximal muscle weakness	1	1	4	1	1
Constitutional symptoms					
Prolonged fever	1	1	1	4	1
Prolonged fatigue	1	1	1	4	1
Asthenia	1	1	1	4	1
Prostration	1	4	1	4	1
Hepatic					
Jaundice	1	1	1	2	2
Ocular/visual incapacity	1	4	1	4	1

* Level of attribution 1 = not related (or not described); 2 = unlikely; 3 = possible; 4 = probable; 5 = most probable ** Late deaths possibly related to treatment (Level 3). †GIT = gastrointestinal tract

parasites do not appear to contribute significantly to increased morbidity [56].

Other factors

Suramin has important intrinsic toxicity and some of the deaths during the treatment of onchocerciasis have been difficult to explain. However, a proportion of its adverse reputation in onchocerciasis have been due to a "transfer" of SAEs observed in the treatment of trypanosomiasis and pemphigus [48].

The linkage of SAEs to Causality

The attribution of SAEs to the administered drug or trial product requires a consideration of the following factors:

1) Temporal relationship between the administration of the drug and the adverse event.

2) The known response pattern to the drug

3) The subject's underlying clinical state, other therapeutic intervention and concomitant therapy

4) Response to de-challenge (discontinuation of the drug) and re-challenge (repeat exposure to the drug).

In many of the drug-related SAEs described, re-challenge was not possible, practicable or justifiable. Hence, the highest level of attribution (Level 5 or "most probable"), as defined previously, could not be allocated. Otherwise,

these SAEs are summarised in Table 2, together with the assigned levels of attribution.

Outcome

When the deaths due to over-dosage with suramin and therapeutic misadventures are discounted, drug-related SAEs in the treatment of onchocerciasis rarely include fatalities. SAEs due to the intrinsic toxicity of metrifonate and amocarzine are completely reversible over several days; those due to suramin may last for several weeks. Most of the SAEs associated with the death of microfilariae either resolve spontaneously or respond favourably to therapy within a few days, without any disability or incapacity. The major exception is the effect on the ocular/visual system where visual field loss can be severe (tunnel vision) and irreversible.

Corticosteroids have been used, aided by supportive therapy, in many categories of SAEs. The main indication has been the general status of the patient. Thus, they have been used in patients who are desperately ill or in a state of shock, in patients with multiple episodes of SSPH, in the cerebrotoxicity of amocarzine and for the ulcerative lesions and prostration following suramin therapy. When indicated after microfilaricidal therapy, our practice has been to give a single dose of 200 mg of hydrocortisone sodium hemisuccinate intravenously. Only occasionally has the patient required a second dose. However, with the cerebrotoxicity of amocarzine, this dose was given every 2 hours for 6 to 8 hours. The effect was not as dramatic as with other SAEs. A short course of betamethasone was needed for one of the asthmatics during the OCP studies. Corticosteroid eye drops are needed in the iridocyclitis following DEC or suramin to prevent the formation of adhesions.

The acute polyarthritis of the "secondary phase" responds favourably to paracetamol or aspirin and corticosteroids are not needed. Lymphatic lesions also respond but less promptly. Other drugs used were antihistamines for pruritus and atropine for the abdominal colic of metrifonate.

Conclusions

In the absence of *Loa loa* infection, the treatment of onchocerciasis with Mectizan® rarely results in SAEs. Most of this presentation therefore focused on a systematic review of SAEs following treatment with DEC, suramin, metrifonate and amocarzine. The benzimidazole carbamate derivatives – mebendazole and albendazole – and the antibiotic doxycycline were not considered, as SAEs were never reported. SAEs associated with suramin, DEC and amocarzine were considerable; in some cases, they were fatal. They serve to emphasise the major leap that occurred with the introduction of Mectizan® for the treatment and control of onchocerciasis. Mectizan® has eliminated the use of DEC (except as a diagnostic agent in the "patch test") and left little justification for the use of suramin. The rarity of SAEs with Mectizan® has made community distribution, by those with little more than the capacity to keep records, feasible. Although Mectizan® has the unique ability to eliminate high microfilarial loads with minimal or no adverse effects, serious adverse events do occur occasionally and care is still needed when the heavily infected Mectizan®-naïve are to be treated. The pathogenesis of the adverse effects remains unknown and requires study. The elucidation is likely to be complex because any proposed mechanisms [57–64] need to explain why Mectizan®, a potent microfilaricide, differs so radically from other agents in the onset, course and severity of adverse events, and the lack of "secondary reactions". A practical consideration is how a knowledge of the pathogenesis will impact on the use of Mectizan® in the field.

Competing interests

None

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