

Safety of high-dose ivermectin: a systematic review and meta-analysis

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Background: Ivermectin is a key anthelmintic for the control of neglected tropical diseases. The main indications for population-level control with ivermectin through mass drug administration are onchocerciasis and lymphatic filariasis; however, there is interest in using higher, fixed-dose regimens for the control of scabies, soil-transmitted helminths and malaria. Safety data for these higher-dose regimens are needed.

Methods: A systematic literature review and meta-analysis on the safety and doses of ivermectin was conducted. Eligible studies reported patient-level data and, for the meta-analysis, clinical trials reporting data on doses ≥ 200 and ≥ 400 $\mu\text{g}/\text{kg}$ were included. Incidence ratios were used to compare adverse events by severity and organ system affected.

Results: The systematic search identified six studies for inclusion, revealing no differences in the number of individuals experiencing adverse events. A descriptive analysis of these clinical trials for a variety of indications showed no difference in the severity of the adverse events between standard (up to 400 $\mu\text{g}/\text{kg}$) and higher doses of ivermectin. Organ system involvement only showed an increase in ocular events in the higher-dose group in one trial for the treatment of onchocerciasis, all of them transient and mild to moderate in intensity.

Conclusions: Although within this review the safety of high-dose ivermectin appears to be comparable to standard doses, there are not enough data to support a recommendation for its use in higher-than-approved doses. Ocular adverse events, despite being transient, are of concern in onchocerciasis patients. These data can inform programme managers and guide operational research activities as new approaches for the use of ivermectin are evaluated.

Introduction

Preventive chemotherapy through mass drug administration (MDA) is the main strategic intervention implemented for the control of human helminthiasis on a global scale.¹ The provision of safe and effective drugs to communities with the highest burden in terms of morbidity and prevalence has been demonstrated to be a powerful tool for the programmes aimed at the elimination of onchocerciasis or lymphatic filariasis (LF) and for the control of soil-transmitted helminth (STH) infections and schistosomiasis.^{2–4}

Anthelmintics available through drug donations are being used according to manufacturer recommendations and a large body of experience and knowledge has been gained through their use in millions of individuals.⁵ Ivermectin is probably the most remarkable anthelmintic drug owing to its impact on onchocerciasis and

LF, with an efficacy and safety that have made it the most relevant tool for the control of those diseases.⁶ Beyond its microfilaricidal activity against filarial nematodes, its horizons have been expanded through new findings of significant activity against *Trichuris trichiura* when co-administered with benzimidazole drugs, its efficacy for the treatment of scabies and a potential role in malaria control due to its endectocidal activity against *Anopheles* mosquitoes.^{7–10} As the drug of choice for the treatment of *Strongyloides stercoralis* infections, rising awareness about this STH adds to the increasing demand for ivermectin.^{11,12} These newly defined opportunities in the role of ivermectin as a tool for disease control beyond its original uses is also defining more ambitious public health goals of disease elimination, as is the case for LF, where a triple-drug regimen of albendazole, ivermectin and

diethylcarbamazine citrate has demonstrated its superior efficacy, which has prompted its recommendation in the most recent WHO guidelines for the treatment of LF.^{13,14}

The main obstacles for an expanded use of ivermectin have been its limited supply and the severe adverse events (AEs) (encephalopathy) experienced by patients coinfecting with *Loa loa*.^{15–17} Despite these issues, widespread use has demonstrated that ivermectin is a very safe drug with infrequent and mostly mild AEs.^{5,18} Currently, ivermectin is prescribed at doses of 150–200 µg/kg against most filarial and *S. stercoralis* infections and approved in doses of up to 400 µg/kg against infections with *Wuchereria bancrofti*.^{19,20} Among the new indications under evaluation for ivermectin like STH and malaria control, doses >400 µg/kg are being evaluated with the purposes of improving efficacy through the achievement of higher peaks and/or extending the intervals with detectable drug levels.²¹ With the aim of simplifying the implementation of MDA activities, the potential use of ivermectin at a fixed rather than a weight- or height-based dosing regimen is under evaluation, in order to lead to coformulations with drugs like albendazole or mebendazole, which are prescribed as fixed-dose regimens. Provided it can demonstrate a proper safety profile, high-dose ivermectin would allow large groups of the population to be adequately treated with just a few, or even a single, fixed-dose formulation of ivermectin. In a recent study using 18 mg ivermectin tablets, a safety and pharmacokinetic (PK) trial in 54 healthy adult volunteers demonstrated the possibility of using fixed-dose regimens of 18 and 36 mg.²² The aim of this study was to systematically review the safety profile of high-dose ivermectin in order to contribute to the exploration of opportunities for expanded uses of this drug.

Methods

The study protocol was registered with the Prospero International Prospective Register of Systematic Reviews on 11 November 2017 (CRD42017078101).

The review question was to assess the safety of ivermectin in humans when used at doses of >200 and >400 µg/kg/day, regardless of the duration of the treatment.

Search strategy and selection criteria

A systematic literature search was carried out in several databases from inception until January 2018. The following databases were searched for relevant studies: MEDLINE (PubMed); Web of Science Core Collection; Cumulative Index to Nursing and Allied Health Literature (CINAHL database); Tropical Diseases Bulletin; CAB Direct; Scopus (Elsevier API); Science Direct; International Pharmaceutical Abs (Ovid); and Conference Papers Index (CSA) (ProQuest XML).

All relevant studies were reviewed, regardless of language or publication status (published, unpublished, in press and ongoing). The reference lists of all included studies for other potentially relevant research and authors' personal collections (grey literature) were also reviewed.

Search terms

Searches were conducted by combining the following three groups of terms: (i) ivermectin; (ii) dosage 400, 600, 700, 800, high-dose, high dose; and (iii) adverse effects, side effects. Studies were filtered to include only human studies (Table S1, available as [Supplementary data](#) at JAC Online).

Authors of recently published abstracts and manuscripts in press were contacted to retrieve full articles.

Selection of studies

Two reviewers (M.N. and D.C.) independently reviewed the titles and abstracts yielded by the search and identified all studies that potentially met the inclusion criteria for this review. Thereafter they independently assessed whether each study met the inclusion criteria using an eligibility form. When the reviewers did not initially reach a consensus, a third reviewer (A.R.-M.) made the final inclusion decision. All excluded studies were documented with their reason for exclusion.

We included all studies evaluating the safety of ivermectin in humans, including case-control studies. For studies that evaluated the administration of ivermectin at high doses co-administered with other drugs, we tried to disaggregate the data or we contacted study authors to request disaggregated data. In the systematic review we included all studies on patients receiving ivermectin regardless of the indication; however, the underlying condition was recorded. Studies conducted on immunosuppressed patients were also considered for inclusion. Further, we performed a meta-analysis including studies where a group of participants receiving higher doses was compared with a control group (participants receiving standard doses).

Data extraction and data analysis

Two reviewers (M.N. and D.C.) independently performed data extraction using a pre-designed data extraction form. They resolved any disagreements regarding the data extraction by discussion between the two reviewers. When necessary, a third reviewer (A.R.-M.) facilitated discussion until consensus was reached. They entered the extracted data into an Excel database (Microsoft, Redmond, WA, USA).

Data about the study design, study population (including number of individuals, whether patients or healthy individuals), inclusion and exclusion criteria and statistical methods were collected. The analysis was done stratifying between those using any doses >200 µg/kg and those using any doses >400 µg/kg. The reference standard was a dose of ivermectin of 150 to 200 µg/kg. The primary outcomes were the AEs of ivermectin at doses >200 µg/kg and >400 µg/kg (as ivermectin doses up to 400 µg/kg are indicated for some pathologies such as LF) compared with standard doses.

For the meta-analysis, we considered for inclusion only studies where the following information was available: (i) the absolute number of patients treated with standard dose and higher doses; and (ii) the absolute number of patients who experienced any AE, both in the standard-dose arm and in the higher-dose arm. The AEs reported were considered drug related unless specifically attributed and documented to other causes in the publication. A descriptive analysis was performed in relation to the type (ocular, neurological, cutaneous and other AEs) and grading (mild, moderate, severe, life-threatening) of AEs, ivermectin indication, age (older/younger than 15 years), different study setting (by geographical continent), clearing dose (administration of a standard 150 µg/kg dose 3 months before the high dose, in order to reduce the risk of ocular AEs in subjects with high ocular microfilarial densities) and single versus multiple dosing.

Quality assessment

All studies included in the meta-analysis were randomized clinical trials (RCTs). The methodological quality of these studies was assessed using the NICE methodology checklist for RCTs.²³ In studies subject to risk of bias, and lacking information, we contacted the corresponding authors in order to attempt to obtain missing data and clarify unclear methodology. Two reviewers independently assessed the quality of the studies included in the meta-analysis (M.N. and D.C.). The report of the systematic review followed the PRISMA-harm checklist, specific for systematic reviews including harm outcome (Table S2).

Statistical analysis and data synthesis

The absolute frequencies of any AE related to drug use in each treatment group were extracted from all considered studies. First, ORs for the association between any AE and higher-dose treatment with ivermectin were calculated for each study, together with their corresponding 95% CIs. The Cochran–Mantel–Haenszel method with random effect was then used to obtain a pooled estimate of the effect of higher-dose treatment. Measures of heterogeneity such as the I^2 and the DerSimonian–Laird estimator for τ^2 were also calculated. Forest plots were used to illustrate the point estimate with 95% CI. Such meta-analysis was performed using R version 3.4.3 (meta package). Incidence ratios (IRs) were calculated for comparisons between dosing groups in terms of AE severity and organ system involvement.

Results

Included studies

The search strategy yielded 452 studies after removing duplicates. The authors identified six additional studies with relevant information for the systematic review that were included and assessed for eligibility. Two hundred and ninety-two studies were excluded after reading the title because they did not address our questions (studies about other topics, studies on animals, non-oral ivermectin) and, when any doubt remained, abstracts and/or whole articles were scanned; 109 were excluded after reading the abstract (mainly

because they were reviews, case reports or about standard-dose ivermectin) and 48 were excluded after examining their full text. Nine of the 452 studies met the selection criteria. Finally, six studies were included for the meta-analysis (Figure 1).^{21,22,24–27}

Quality assessment

The quality of the studies was evaluated; regarding allocation, half of the six studies showed unclear methods of randomization^{22–24} and an adequate concealment of allocation was confirmed in only three.^{18,24,25} Baseline characteristics of study groups were comparable in all but one study, which was a paediatric study not balanced for gender.²⁷ Three of the six studies were described as double-blind RCT.^{18,22,24} The study by Wimmersberger *et al.*²⁷ was a single-blind RCT and the two remaining trials were open-label RCTs (Dembele *et al.*²⁴ and Muñoz *et al.*²²). Consequently, risk of bias should be considered due to investigators' lack of blindness to participants' intervention and to other confounding and prognostic factors. Moreover, lack of blindness of participants to allocation was detected in two of the studies.^{22,24} Blindness of individuals administering care was lacking in three of the studies.^{22,24,27}

Regarding the received care and the length of follow-up between study groups, no risks of bias were detected in any of the manuscripts included. Treatment completion was comparable

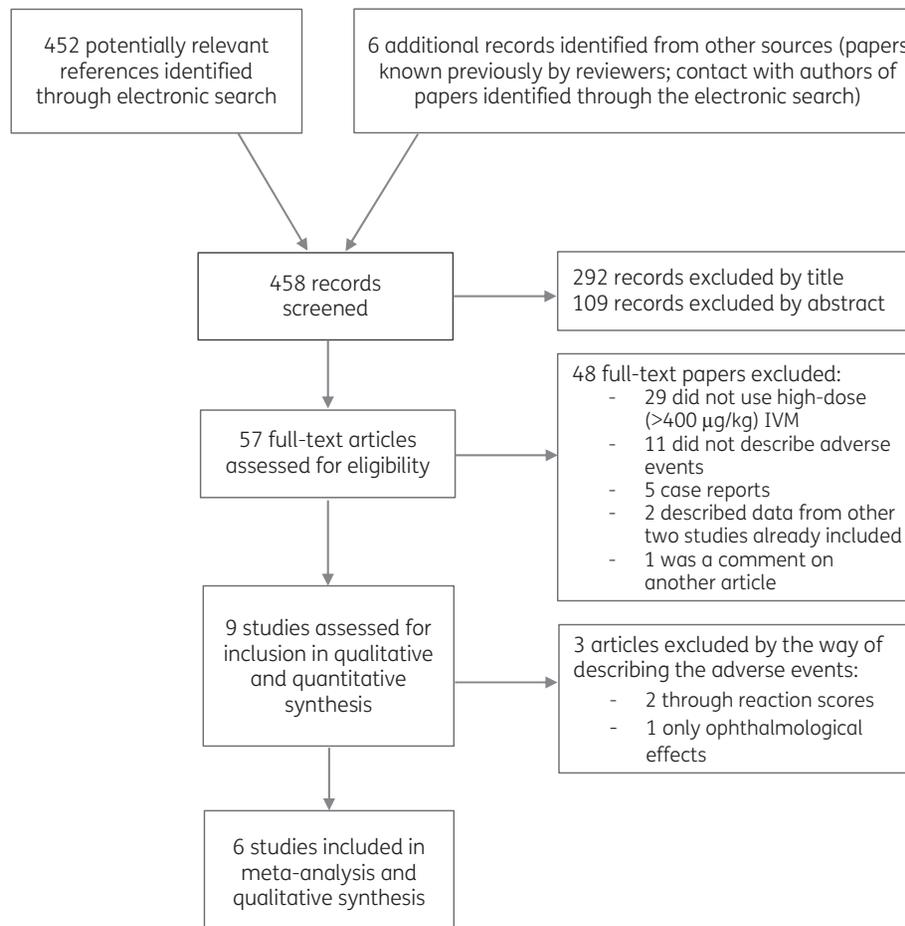


Figure 1. PRISMA flow diagram of systematic literature search. IVM, ivermectin.

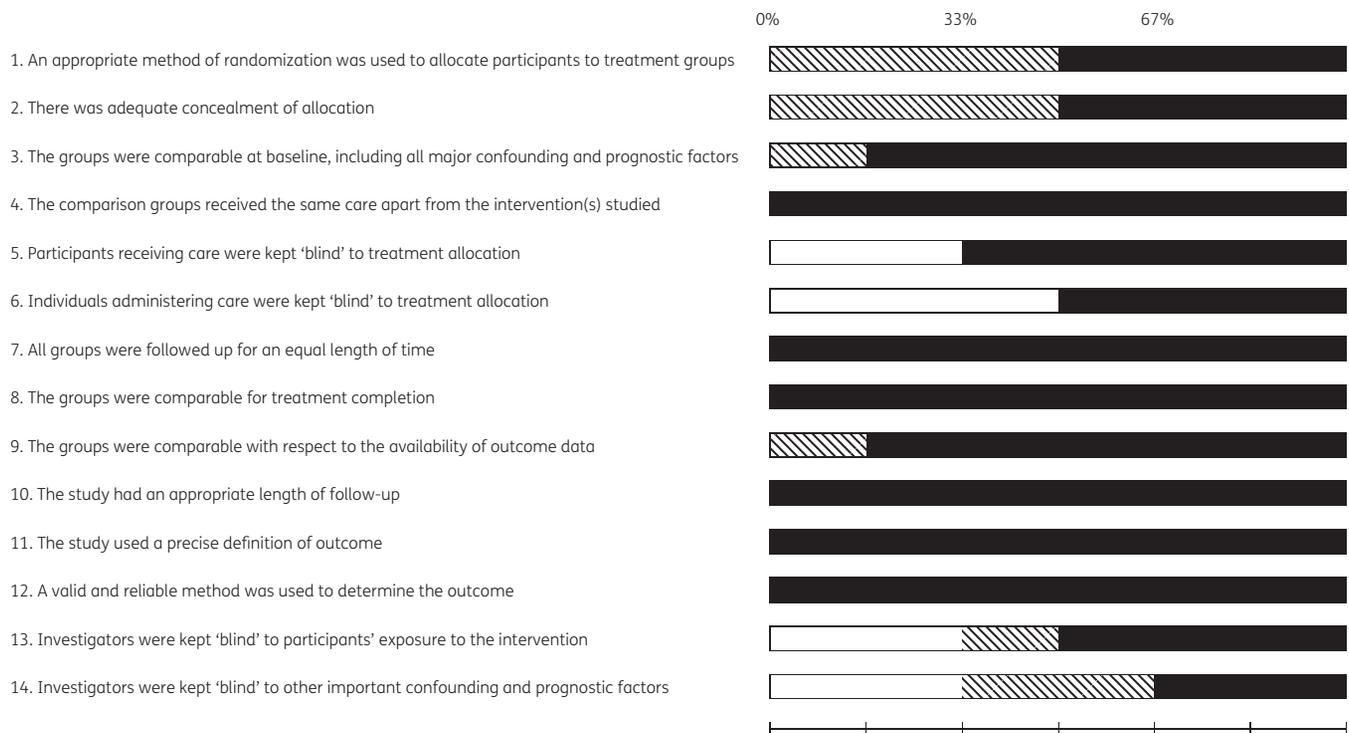


Figure 2. Quality assessment of the studies included in the meta-analysis using the NICE Methodology Checklist for RCTs. White, 'no'; striped line, 'unclear'; black, 'yes'.

between study groups in all articles. All studies included used a precise outcome definition and a reliable method to determine the outcome. Regarding risk of selective reporting bias, outcome data were comparable between study groups in all articles except those in which these data were unclear.²⁶ Length of follow-up was considered appropriate in all studies. The overall risk of bias is presented graphically in Figure 2.

Descriptive analysis

The four studies included in the meta-analysis with doses either up to 400 µg/kg or higher doses were also analysed in order to describe the total number of AEs, their severity and the involvement of particular organ systems (Table 1). In this analysis that included trials for diverse indications, including healthy volunteers, the high-dose arm included doses of up to 800 µg/kg. Since trial participants could experience more than one AE, IRs were calculated to evaluate the involvement of particular organ systems (ocular, neurological and cutaneous) most frequently described in the literature in the safety profile of ivermectin, revealing in just one clinical trial, for the treatment of onchocerciasis,²⁶ a significant increase in AEs related to the ocular system (IR 2.797, 95% CI: 1.226–6.377). Ocular AEs evaluated in this trial were subjective ocular symptoms such as transitory blurring of vision, itching or pain of the eye and dyschromatopsia. Severity of AEs showed that all studies reported 100% of the AEs as mild or moderate in both arms (standard and high dose), with serious AEs, described as life-threatening, reported in just one study with one case in the standard dose (anaphylactic reaction) and another in the high-dose group (QTc prolongation in the ECG, most likely due to a

concomitant drug).²¹ All studies were performed in Africa except one that was performed in Europe in healthy volunteers.²² Ages of treated patients/individuals ranged from 2 to 60 years; one of the studies was performed in children (2–12 years) and the rest among adults (>18 years). Only one study administered a clearing dose of 150 µg of ivermectin before treatment.²⁶

Meta-analysis

A total of six studies qualified for the different meta-analyses. Five studies published between 1993 and 2018 were included in the meta-analysis using 400 µg/kg as the cut-off, with moderate heterogeneity ($I^2 = 39\%$).^{22,24–27} The random-effects model was 1.06 (95% CI 0.67–1.69), showing no difference between the study arms (Figure 3a). The meta-analysis was then repeated to compare ivermectin doses up to 200 µg/kg with higher doses. In this case, the analysis included four studies,^{21,22,26,27} for which the results showed no difference in OR between study arms, according to both fixed and random-effects models; in this case, the random-effects model was 1.16 (95% CI 0.89–1.52) with very low heterogeneity (Figure 3b).

Discussion

This study describes the safety of ivermectin when used at higher daily doses than the standard regimens through the oral route of administration in humans. The methodological approach using a systematic review of the literature and meta-analysis allowed the comparison and joint analysis of different published trials using diverse underlying clinical conditions including healthy volunteers.

Table 1. Descriptive analysis of AEs of ivermectin by organs and systems in clinical trials comparing standard (up to 400 µg/kg) versus high-dose (>400 µg/kg) ivermectin

Condition under study	IVM dosage (µg/kg) ^a	Follow-up	AE/N	OR (95% CI)	n	Ocular		Neurological		Cutaneous		Other		Reference
						n	IR (95% CI)	n	IR (95% CI)	n	IR (95% CI)	n	IR (95% CI)	
Onchocerciasis														
high dose	800	3 years	149/172	1.135	13	2.797	25	0.960	63	1.369	48	0.956		26
standard dose	150-400		273/370	(0.834-1.545)	10	(1.226-6.377)	56	(0.599-1.539)	99	(0.998-1.877)	108	(0.681-1.343)		
Healthy volunteers (PK)														
high dose	401-700	7 days	8/49	0.907	0	—	2	0.512	0	—	6	1.258		22
standard dose	200-400		20/113	(0.369-2.228)	0		9	(0.111-2.372)	0		11	(0.465-3.401)		
Trichuriasis														
high dose	600	3 days	9/33	1.346	0	—	2	1.018	1	1.018	6	1.328		27
standard dose	100-400		38/168	(0.532-3.405)	0		10	(0.223-4.647)	5	(0.119-8.715)	23	(0.541-3.261)		
Malaria														
high dose	600	28 days	13/45	3.286	4	2.133	2	1.067	0	—	7	2.489		21
standard dose	300		7/48	(0.951-11.355)	2	(0.391-11.648)	2	(0.150-7.573)	0		3	(0.644-9.625)		

IVM, ivermectin; N, number of participants in each treatment group.

^aHigh (>400 µg/kg) and standard (≤400 µg/kg) doses are defined based on the study definition of this analysis, which may differ from the categorization of high and standard doses for each individual study by the authors of these publications.

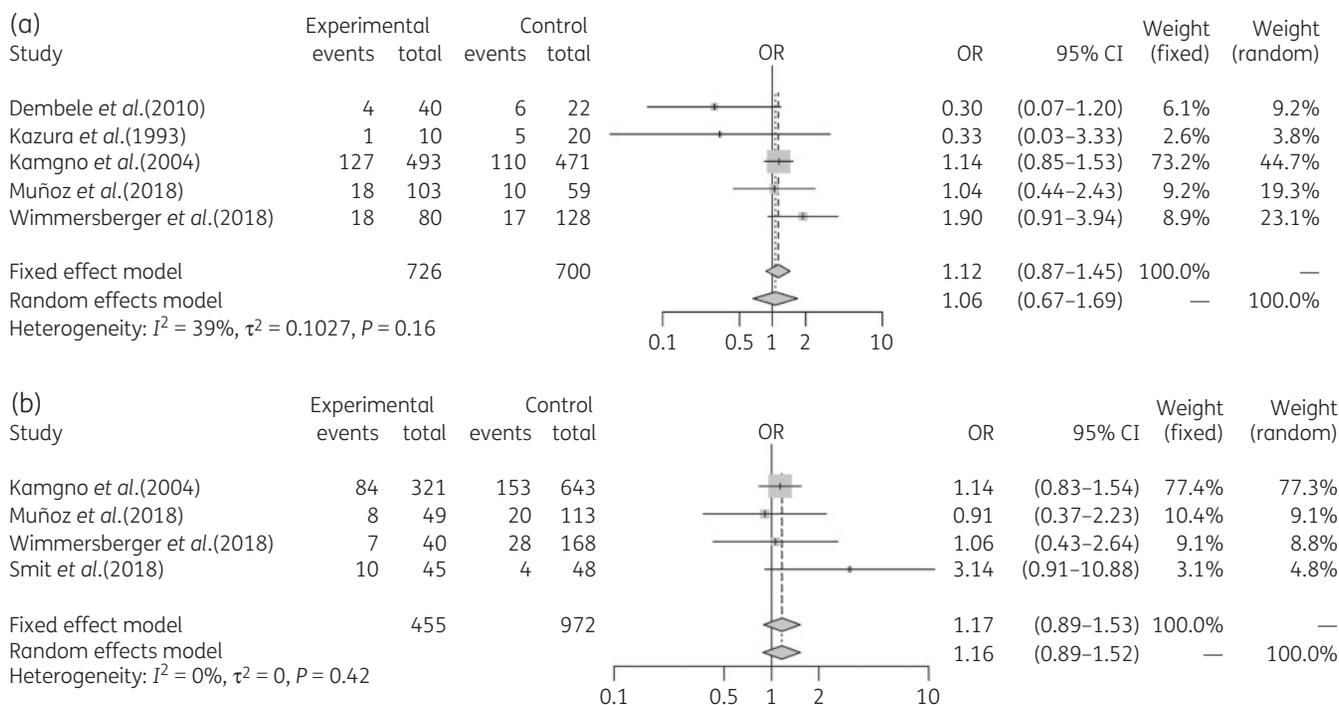


Figure 3. Meta-analysis of the association between AEs and standard- versus high-dose ivermectin using standard doses of 400 µg/kg (a) or 200 µg/kg (b) as reference.

Since the aim of the study was to understand the safety profile of higher doses of ivermectin to allow the consideration of their use at higher doses, in order to achieve higher efficacy or as a path to fixed dosing as an alternative dosing regimen to the weight-based approach currently recommended, the comparator of choice was the safety at regular doses (up to 400 µg/kg), which are well

known, rather than comparing the safety of higher doses to that of placebo or no treatment. Through this approach, a fixed-dose regimen would provide a variable amount of µg/kg of ivermectin, therefore exposing a significant proportion of individuals to doses higher than those in the usual regimens. A proper understanding of the safety of these higher doses, which offer potential

advantages in the prevention of the emergence of drug resistance, is for this reason necessary.²⁸

For the purpose of the meta-analysis, the treatment regimens were grouped into two arms, but it should be considered that in the 'higher doses' arm we had a wide range of doses. Although it was not possible to analyse further the influence of increasing doses of ivermectin, the results here do not suggest a trend in increasing AE with increasing doses. Only one study in patients with onchocerciasis demonstrated a higher risk of AE in the higher ivermectin-dose group,²⁶ which in further analysis was not able to link these AEs to microfilaraemia or disease-related lesions.²⁹ The most common complaints were transient blurred vision, itching or pain in the eye, scotomas or seeing flashes of light, all of them disappearing gradually over a few days. Another study included in our analysis found a non-significant increase in transient minor visual disturbances between subjects receiving 600 µg/kg compared with those receiving 300 µg/kg.²¹ These findings are consistent with previous reports concluding that the type and severity of the underlying conditions is the most relevant variable that determines the safety of ivermectin.³⁰ Notably, the safety profile and AEs of ivermectin are generally not dose-related, as shown in a study that determined no relationship between serum ivermectin drug levels at 24 and 48 h post-administration and AEs among 71 patients with onchocerciasis.³¹ In a clinical trial for the treatment of onchocerciasis, incremental doses of up to 800 µg/kg of ivermectin showed equal results in both efficacy and safety;³² still, in a large intervention for onchocerciasis with over 50 000 treated individuals receiving between 130 and 200 µg/kg, there was a statistically significant relationship between the incidence of all reactions and ivermectin dosage after correction for microfilarial load, although no such relationship existed for moderate or severe reactions.³³ The limited number of studies that qualified for this review did not permit us to conduct subanalyses, for instance evaluation of the possible influence of underlying conditions in the development of AE or the geographic location of the trial.

The findings, although limited by the small number of studies and lack of blinding, add evidence to the safety of ivermectin at doses up to 800 µg/kg, which demonstrated an overall comparable safety to standard doses, which in this meta-analysis was tested in separate analyses using the 200 and 400 µg/kg doses as the highest standard dose since, for *W. bancrofti* infections, 400 µg/kg has been used for MDA campaigns.³⁴ Moreover, AEs observed in both groups were entirely of mild or moderate intensity. Remarkably, the largest study included in this analysis, which was performed in individuals with onchocerciasis, describes previously unpublished data of AEs categorized by the affected organ system revealing an increased IR for events affecting the vision with an IR of 2.80 (95% CI: 1.23–6.38) (Table 1). AEs categorized as systemic, neurological and cutaneous were present without significant increased frequency between groups. All other studies included in this analysis did not show a statistically significant increased risk of visual disturbances between groups. Some subjective ocular troubles (transitory blurring of vision, itching or pain of the eye and dyschromatopsia) appeared, but no patient developed any severe AE and none withdrew from the trial because of an adverse reaction. These results agree with a recent review of studies evaluating AEs in the treatment of LF, identifying the level of microfilaraemia rather than drug or dose as the variable most related to toxicity.³⁰ In a study including a limited number of healthy volunteers

receiving doses up to 2000 µg/kg (10 times the recommended doses), ivermectin was well tolerated and ocular AEs were similar to those with placebo.³⁵

With over 30 years of ample use and over 300 million people using it annually, ivermectin is, through its use in MDA campaigns, among the most relevant public health interventions in the developing world.³⁶ Despite this wide experience, there are still concerns and areas in need of evidence for a better understanding of the safety of ivermectin in order to expand its benefits to new indications and groups, like pregnant women and children <15 kg. The lack of safety data among these population groups results in their exclusion from MDA campaigns. However, recently published PK data from children receiving ivermectin for *T. trichiura* infections showed lower exposure profiles than adults receiving similar doses of 200 µg/kg, therefore suggesting that higher doses might be necessary in this age group.³⁷ A recent analysis of the databases of an international pharmacovigilance system concluded that even at regular doses, neurological serious AEs are rare without *L. loa* infections but research on other risk factors for these AEs is still needed.³⁸ Other relevant aspects for the understanding of PK/pharmacodynamic parameters of ivermectin are those related to the relationship of PK parameters, mostly C_{max} , with the appearance of toxicity. The high variability in PK parameters observed in humans may mask the effect associated with increased exposure if clinical trials are not accompanied by PK data.²² In that study, the parameters related to drug exposure (AUC and C_{max}) showed a high interindividual coefficient of variation (CV) (CV = 37.4% and CV = 32.5%, respectively) and intraindividual variability (CV = 39.6% and CV = 33.2%, respectively),²² therefore placing limitations on the results and conclusions from studies based purely on the relationship between dose and AEs.

While this study used the daily rather than multiple-day cumulative doses of ivermectin as the unit of analysis, this approach is based on the little variation seen in the daily C_{max} of ivermectin over three doses of up to 600 µg/kg on consecutive days.³⁹

Conclusions

This systematic review, including a meta-analysis, has shown that AEs following single-dose treatment with up to 800 µg/kg of ivermectin occur without significant differences of frequency or intensity to those at regular currently approved doses. Ocular AEs, despite being transient, are of concern in onchocerciasis patients, requiring caution and further studies if ivermectin is used at high doses for that indication. The AEs reported in the reviewed studies were mostly mild or moderate in nature, suggesting the safety of ivermectin. There is, however, a paucity of information able to be analysed and a lack of blinding in the studies included, therefore calling for consensus in the proper and standardized manner of reporting safety data, as has been suggested by other groups,³⁰ in order to have adequate information to provide to the programmes and healthcare workers participating in MDA campaigns on the management of AEs related to ivermectin. To conclude, more clinical trials evaluating the safety of ivermectin at higher doses, and in children <15 kg and pregnant women, are needed.

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Transparency declarations

None to declare.

Authors contributions

M.N.: First reviewer of all the papers and systematic review, leading analysis and writing; D.C.: Second reviewer of all the papers and systematic review, analysis of descriptive results; A.R.-M. Study design, conceptualization, third reviewer for discordant results and quality assessment; D.B.: Meta-analysis design; G.G.: Meta-analysis, statistics and graph; J.K.: Data processing; J.G.: Data processing; M.B.: Data processing; J.M.: Conceptualization and results interpretation; A.K.: Original idea, design, analysis and writing.

Disclaimer

The views and opinions of authors expressed herein do not necessarily state or reflect those of EDCTP.

Supplementary data

Tables [S1](#) and [S2](#) are available as [Supplementary data](#) at JAC Online.

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