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ORIGINAL ARTICLE

Ocular toxoplasmosis: adverse reactions to treatment in a Brazilian cohort

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Background: The purpose of this study was to estimate the frequency and describe the adverse drug reactions (ADRs) associated with the classic treatment of ocular toxoplasmosis (OT), namely sulfadiazine, pyrimethamine, corticosteroids and folinic acid.

Methods: We performed a descriptive study of a prospective cohort of patients with OT treated with the classic therapy. Data were collected during medical consultations and treatment.

Results: Of the 147 patients studied, 85% developed one or more ADR. Women presented more ADRs than men (95% vs 77%). Of the total reactions (n=394), 82% were mild, but we found one life-threatening event (Stevens–Johnson syndrome). The most frequent types (71%) of ADRs were gastrointestinal, skin and neurological or psychiatric. The majority of ADRs (90.3%) occurred before the second week of treatment. A third of the patients were treated for the ADR and 10% dropped out of OT treatment. Most (70%) of the ADRs were characterized as being probably caused by the drugs and may be associated with prednisone, sulfadiazine and sulfadiazine/prednisone. Six percent of ADRs were not previously described, such as taste alteration, constipation/bloating, dyspnoea, sweating and somnolence.

Conclusions: Our results suggest a high rate of ADRs to OT classic treatment, which requires careful follow-up in order to identify and treat ADRs early.

Keywords: adverse drug reactions, drug therapy, ocular toxoplasmosis, uveitis

Introduction

Toxoplasmosis is a zoonosis that infects approximately one-third of the human population worldwide and has a great diversity of clinical manifestations. Ocular toxoplasmosis (OT) may be associated with acute acquired or congenital infection and is the most common form of posterior infectious uveitis.[1,2] Typical toxoplasmic retinochoroiditis is an area of active retinitis adjacent to a pigmented scar.[3]

Current treatment approaches for OT are still controversial.[4,5] Toxoplasmosis is a multi-organ infection and it is frequently a management challenge for both specialists in infectious diseases and ophthalmologists. Some authors recommend treatment in all cases,[4] while others indicate treatment based on the location and extent of the lesions.[6] Impaired visual acuity results from the intensity of vitreous inflammation or involvement of the macula and optic disc. The development of permanent visual impairment may be due to synechia, optic nerve atrophy or macular scar.[7,8] Recurrences can cause progressive loss of vision and there is still no treatment to prevent their development.[4,9]

Treatments for OT include different antimicrobials, including sulfadiazine, pyrimethamine, clindamycin, azithromycin and cotrimoxazole. Sulfadiazine, pyrimethamine, corticosteroids and folinic acid is the most commonly used combination of drugs and is considered the classic therapy for this disease.[1,2] However, none of the drugs available fulfils the requirements for the ideal treatment of OT, including being parasitocidal (i.e., effective against all evolutionary stages of the parasite), reaching therapeutic concentration inside the ocular globe, being safe, reducing the incidence of recurrences and avoiding permanent visual damage.[4,10] Myelotoxicity,[11] cutaneous lesions,[12] nephrotoxicity,[13] allergic reactions,[14] digestive intolerance,[15] osteoporosis,[16] diabetes,[17] hydric retention,[18] high blood pressure[19] and irritability[20] are some of the adverse drug reactions (ADRs) associated with the use of these drugs individually.

Nevertheless, there are only a few studies of ADRs associated with their use as a combination therapy.[6,7]

The aims of this study were to estimate the frequency and describe the ADRs associated with the classic treatment of OT. Recognition of the safety of the treatment for OT may contribute to better identification of patients who will actually benefit from the treatment and thus enable better control of its potential risks.

Materials and methods

This is a descriptive study of a cohort of 147 patients with OT who attended a reference centre for ocular infection. The sample considers the prevalence of *Toxoplasma gondii* infection in the population (70%),[21] ocular lesions associated with acute acquired toxoplasmosis (20%)[2] and ADRs associated with OT treatment (40%).[6] The statistical significance was set at 0.05.

Eligible patients were recruited between November 2011 and December 2013 from the outpatient unit of the Research Laboratory of Ophthalmology in Infectious Diseases, Evandro Chagas National Institute of Infectious Diseases, Fiocruz, Rio de Janeiro, Brazil. Patients of both sexes with typical toxoplasmic retinochoroiditis (active foci of retinochoroiditis satellite to a pigmented scar) were sequentially included. Patients were prescribed the classic oral treatment for OT: pyrimethamine (100 mg loading dose on the first day, followed by 50 mg daily), sulfadiazine (1 g every 6 h), folinic acid (5 mg daily) and prednisone (40 mg daily with progressive dose reduction). The clinical monitoring of ocular lesions was undertaken by regular medical consultations at the outpatient unit until healing.[5] Patients were excluded if they had atypical lesions, were younger than 12 y, were pregnant or had any of the following comorbidities: human immunodeficiency virus infection, cancer, chronic renal failure, transplants, use of immunosuppressive drugs or addiction to alcohol or drugs.

Sociodemographic (sex, age) and clinical data (comorbidities, drugs used, ADRs) were collected during the medical consultations and by telephone interviews. A standardized and pretested form was developed to collect the data.

ADRs, defined as 'a response to a drug that is noxious and unintended and occurs at doses normally used in man for the prophylaxis, diagnosis, or therapy of disease',[22] were registered through telephone interviews conducted by two trained researchers between days 7 and 10 of therapy and at the end of the treatment. During the interviews the patients were asked to report any symptom that presented during the treatment, the date of its emergence and duration and the use of concomitant medications. Patients who reported ADRs were referred for medical consultation by one of the investigators and treated at the outpatient unit or hospitalized at the same institution according to the need and severity of the case.

The identified ADRs were classified by the organ system affected according to the World Health Organization Adverse Reactions Terminology[22] and described according to the type, period of occurrence and severity. The severity was classified according to the scale of the Division of AIDS of the National Institutes of Health into mild, moderate, severe or life-threatening.[23]

The likelihood of adverse reactions caused by the drugs was analysed with the aid of the Naranjo algorithm, which contains 10 questions, each receiving its own score, addressing the following: compatibility between when the reaction appeared and when the drug was taken, the nature of the reaction, the drug's pharmacological characteristics and alternative causes. The algorithm enables ADRs to be classified as 'definite', 'probable', 'possible' or 'doubtful'.[24] To answer the Naranjo questions, a search of the scientific literature was performed to identify the association of each ADR reported in the study and the drugs used in the OT classic treatment. Therefore these drugs were considered suspected by the ADR. In addition, clinical data previously collected by telephone interviews and medical consultations were used.

Statistical analyses were performed considering patients and ADRs as units of analysis, presenting the data as absolute values and proportions. The behaviour of medians and quartiles of continuous variables was also verified. Differences between proportions were tested using Pearson's χ^2 test and Fisher's exact test considering a significance level of 0.05. Data were entered into Epidata 3.1 (www.epidata.dk) and analysed using the R statistical package, version 3.3.0 (R Project for Statistical Computing, Vienna, Austria).

Results

The ages of the 147 patients included in the study ranged from 13 to 68 y (median 33). Of the participants, 82 (55.8%) were male, the majority were young adults between 18 and 30 y old (42.2%) or adults between 31 and 59 y old (51.7%) and 76 had no comorbidities (n=133 [90.5%]) (Table 1). The median treatment duration was 33 d (interquartile range 28–45.5). Of the 147 patients included, one had two episodes of OT and was considered separately. All patients achieved resolution of ocular lesions during the study period.

In the study sample, 125 (85%) patients developed one or more ADRs. Of these, 23 (15.6%) developed only one ADR, while 102 developed two or more ADRs during the study period. The proportion of ADRs among women was greater than among men (95% vs 77%; p=0.003). All patients who were >60 or <18 y of age, those with comorbidities and those who used more than two concomitant medications developed ADRs (Table 1).

We found 394 ADRs. The majority (82%) were classified as mild in severity, but we found one life-threatening event (Stevens–Johnson syndrome). The ADRs affected the gastrointestinal system (26.6%), psychiatric function (17%), skin and appendages and central and peripheral nervous system (13.7% each) (Table 2). The majority of the ADRs (90.3%) occurred before the second week of treatment.

Among the patients with ADRs, 43 (34.4%) received drug treatment for the reactions. The most frequent ADRs treated were epigastric pain (18 patients [41.9%]), treated with drugs for acid-related disorders; headache (13 patients [30.2%]), treated with analgesics; and drug-induced skin disorders (8 patients [18.6%]), treated with systemic antihistamines. Fourteen (9.5%) patients interrupted the toxoplasmosis treatment. Three of them stopped OT treatment because of the severity of the reactions (hepatotoxicity and cutaneous adverse reactions to drugs)

Table 1. Characteristics of OT patients by occurrence of ADRs to drug treatment, INI/FIOCRUZ, Rio de Janeiro, Brazil, 2011–2013

Patient characteristics	With ADR, n (%)	Without ADR, n (%)	Total, N (%)
Gender			
Male	63 (76.8)	19 (23.2)	82 (55.8)
Female*	62 (95.4)	3 (4.6)	65 (44.2)
Age group (y)			
12–17	5 (100)	0	5 (3.4)
18–30	51 (82.3)	11 (17.7)	62 (42.2)
31–59	65 (85.5)	11 (14.5)	76 (51.7)
≥60 y	4 (100)	0	4 (3.4)
Comorbidities			
None	112 (84.2)	21 (15.8)	133
1	12 (92.3)	1 (7.7)	13
≥2	1 (100)	0	1
Concomitant drugs			
None	113 (84.3)	21 (15.7)	134
1	6 (85.7)	1 (14.3)	7
≥2	6 (100)	0	6
Total	125 (85)	22 (15)	147

*p<0.01.

and were hospitalized. The interruption was temporary in five cases. Two of these resumed the original therapy after treatment of the ADR (epigastric pain and urticaria) and sulfadiazine was replaced with clindamycin in three patients. Treatment dropout occurred in six cases.

The likelihood that the ADR was related to the drugs was analysed using the Naranjo algorithm. The results showed a predominance of probable reactions (70%), followed by possible reactions (30%).

ADRs may be associated with more than one drug. In the study sample, 138 ADRs (35%) were attributed to prednisone, 122 (31%) to sulfadiazine, 91 (23.1%) to the combination of sulfadiazine and prednisone, 13 (3.3%) to pyrimethamine and 6 (1.5%) to the combination of pyrimethamine and sulfadiazine. Twenty-four ADRs (6%) were not previously described in the literature: taste alteration (n=5), constipation/bloating (n=4), dyspnoea (n=4), sweating (n=4) and somnolence (n=4) (Figure 1).

Discussion

Irreversible visual damage caused by OT can be prevented by classic therapy, although peripheral lesions may also reach spontaneous resolution in the absence of treatment. Even though the combination of sulfadiazine, pyrimethamine and corticosteroids is considered the classic and most effective treatment for OT,[3] the effectiveness of this treatment has yet to be proven in controlled trials.[25] Our study showed a high rate of adverse reactions to the classic treatment in the study population. A third of the patients was treated for the adverse reactions and 10% stopped the treatment. Evidence for the efficacy and safety of alternative drugs is scarce. There are few studies and studies including only a small number of patients assessing alternative treatments schedules.[4,5]

The age and sex distributions of the population and the average length of treatment were consistent with the profile of patients with OT described in other studies.[26] Similarly, the inclusion of only cases with gold standard lesion patterns in this study may be the reason for the consistency of our results.

Although the drugs used in the treatment of OT have long been utilized for antimicrobial therapy, there is little known about the safety of combination treatment with these drugs. There has been only one other study designed exclusively to evaluate the incidence and types of ADRs associated with OT treatment, but that study included a smaller number of cases (55 vs 147) and used five drugs (atovaquone, clindamycin, pyrimethamine, sulfadiazine and trimethoprim–sulfamethoxazole) in different combinations.[6]

It should be noted that only 15% of our patients did not develop an ADR and the majority (81.6%) of those who developed an ADR had two or more different reactions (i.e., 125 patients developed 394 ADRs). In Iaccheri's study,[6] fewer total ADRs were observed (22 patients developed 27 ADRs). The lower frequencies and numbers of ADRs observed by the cited study could be attributed to the differences in the designs of both studies, such as the retrospective approach adopted by Iaccheri et al. vs. the prospective approach in our study.

Paediatric[27] and geriatric patients[28] and women[29] are classically at risk for the development of ADRs. In our study, the majority of the patients with ADRs were women, and although we had a small number of patients <18 and >60 y of age, all of them developed ADRs. This suggests the relevance of careful treatment monitoring in those patients.

The most frequent types of ADRs in our study were gastrointestinal, skin and neurological or psychiatric, comprising 71% of the total reactions. Haematological ADRs[6,26] in our study represented only 1% (four cases) of the total ADRs. As in Iaccheri et al.'s study,[6] the majority of ADRs in our study occurred during the first 2 weeks of treatment.

Although the majority of ADRs were mild, 43 patients (34.4%) received treatment for ADRs, which has not been previously described in the literature. Definitive interruption of treatment was required in three (2%) and dropout occurred in six (4%) of the total patients exposed to the drugs. In another study, 7/29 (24%) patients who used pyrimethamine and 10/66 (15%) patients who used sulfadiazine had the drugs withdrawn.[26] The follow-up of patients by periodic telephone interviews and early referral to medical consultation may have contributed positively to the small number of interruptions. Thus early identification and prompt management of ADRs are important to minimize patient suffering and improve treatment outcome.

Our findings permit most (70%) of the adverse reactions to be characterized as being probably caused by the drugs. The Naranjo scale, similar to other causality instruments, classifies the likelihood that a reaction is related to the drug based on concepts including temporal relationships, biological plausibility, rechallenge/previous exposure and alternative causes, such as other diseases and other drugs used.[24] The concomitant use of several drugs, such as in the classic toxoplasmosis treatment,

Table 2. ADRs to toxoplasmosis treatment by severity, organ system affected (WHO-ART) and treatment period, INI/FIOCRUZ, Rio de Janeiro, Brazil, 2011–2013

Type of ADR	Up to week 1, n (%)	Between week 1 and 2, n (%)	Week 3 onwards, n (%)	Total ADRs, N (%)
Severity				
Mild[a]	167 (51.7)	127 (39.3)	28 (8.7)	323 (82)
Moderate	28 (44.4)	29 (46)	6 (9.5)	63 (16)
Severe	1 (14.3)	3 (42.9)	3 (42.9)	7 (1.8)
Potentially life-threatening	0	1 (100)	0	1 (0.2)
Organ system disorder[b]				
Gastro-intestinal system	59 (56.2)	36 (34.3)	10 (9.5)	105 (26.6)
Psychiatric	44 (65.7)	21 (31.3)	2 (3)	67 (17)
Skin and appendages[a]	11 (20.4)	33 (61.1)	9 (16.7)	54 (13.7)
Central and peripheral nervous system	28 (51.9)	21 (38.9)	5 (9.3)	54 (13.7)
Metabolic and nutritional	13 (43.3)	14 (46.7)	3 (10)	30 (7.6)
Musculoskeletal system	16 (64)	7 (28)	2 (8)	25 (6.3)
Cardiovascular[c]	10 (62.5)	4 (25)	2 (12.5)	16 (4)
Autonomic nervous system	6 (50)	5 (41.7)	1 (8.3)	12 (3)
Other[d]	9 (29)	19 (61.3)	3 (9.7)	31 (7.9)
Total	196 (49.7)	160 (40.6)	37 (9.4)	394 (100)

WHO-ART: World Health Organization Adverse Reaction Terminology.
[a]Time was missed for one mild skin and appendage ADR.
[b]WHO-ART.
[c]Including heart rate and rhythm disorders.
[d]Other organ system disorders: respiratory system (n=5); red blood cell, white blood cell, reticuloendothelial system, platelet, bleeding and clotting (n=4); urinary system (n=2); female reproductive (n=1); general (n=8); vision (n=2); other special senses (n=5); liver and biliary system (n=4).

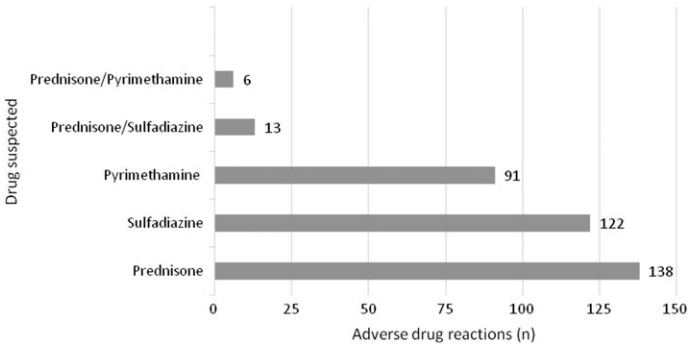

Figure 1. Drugs involved in adverse drug reactions to OT treatment, INI/FIOCRUZ, Rio de Janeiro, Brazil, 2011–2013.

may limit this analysis with an underestimated likelihood of the ADR. However, none of the ADRs registered were classified as doubtful, thereby reinforcing the quality of the ADR reports and confirming the estimates obtained in the study.

Regarding limitations, data collection by telephone interviews is associated with the perception of fewer details and memory bias. However, the use of a standardized questionnaire and two interviews minimized this occurrence. Nevertheless, the results are already quite robust. Another possible limitation could be the time of follow-up until the end of treatment, which could result in the loss of late ADRs.

Conclusions

Our results suggest that the classic treatment for OT requires careful follow-up in order to identify ADRs early and treat them when necessary to minimize patient suffering. The significant proportion of ADRs found in this study corroborates the need for less toxic and more effective treatment options.[30]

Author's contributions: ESN and LG conceived and designed the study and made substantial contributions in interpretation of data and critical discussion of results. BBFV, NMGD and VCL contributed to acquisition and analysis of the data. MSBQ performed the statistical analysis. ALLC contributed to revision of the intellectual content of the manuscript. All authors participated in the critical discussion of the results and contributed to and approved the final manuscript.

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registered in the National System of Information on Ethics in Research (0015.0.009.000-10). Patients provided written informed consent.

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