Profile of adverse events in toxoplasmosis drug therapy: a review
Perfil de eventos adversos na terapia medicamentosa da toxoplasmose: uma revisão
Perfil de acontecimientos adversos en la drogoterapia de toxoplasmosis: una revisión

Received: 10/02/2021 | Reviewed: 10/10/2021 | Accept: 10/18/2021 | Published: 10/20/2021

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Abstract
This study aims to analyze the profile of adverse events (AEs) of drugs for the treatment of Toxoplasmosis. This is a review carried out through a bibliographic search in the electronic databases PubMed, SciELO, Cochrane Digital Library and LILACS. The keywords “Toxoplasmosis” AND “Drug Therapy” AND “Drug-Related Side Effects and Adverse Reactions” were used. The selection was performed by two independent reviewers and the articles were included considering the presence of retrospective studies and case reports published in the literature in Portuguese and English and without time restrictions. In total, 40 articles were found, of which 14 met the inclusion criteria. Cases of cerebral, ocular, gestational and congenital Toxoplasmosis were identified. Among these, we observed a total of 85 patients with reports of AEs due to the use of Pyrimethamine, Sulfadiazine, Spiramycin, Clindamycin, Atovaquone, Trimethoprim and Sulfamethoxazole and Sulfadoxine. Clinical reactions were in the form of skin rash (57.1%), hematological alterations (28.5%), Lyell syndromes (7.1%), Stevens-Johnson (21.4%) and DRESS (21.4%). The prevalence of AEs related to hematological alterations was seen mainly in treatments based on Pyrimethamine + Sulfadiazine, Trimethoprim and Sulfamethoxazole; on the other hand, those associated with severe syndromes are often related to the use of Pyrimethamine + Sulfadiazine. It is important to establish a standard protocol for drug therapy for Toxoplasmosis, which does not yet exist. In addition, the need to monitor patients after drug administration is highlighted, given the possibility of the occurrence of adverse events that can represent a threat to life.

Keywords: Drug-related side effects; Adverse reactions; Drug therapy; Toxoplasmosis; Pyrimethamine.

Resumo
Este estudo tem como objetivo analisar o perfil de eventos adversos (EAs) dos medicamentos de tratamento da Toxoplasmosis. Trata-se de uma revisão realizada por meio de busca bibliográfica nas bases eletrônicas de dados PubMed, SciELO, Cochrane Digital Library e LILACS. Utilizou-se as palavras-chave “Toxoplasmose” AND “Therapy” AND “Drug-Related Side Effects and Adverse Reactions”. A seleção foi realizada por dois revisores independentes e os artigos foram incluídos considerando a presença de estudos retrospectivos e relatos de caso publicados na literatura nos idiomas Portuguêis e Inglês e sem restrição de tempo. No total, foram encontrados 40 artigos, dos quais 14 preencheram os critérios de inclusão. Foram identificados casos de Toxoplasmose cerebral, ocular, gestacional e congênita. Dentre esses, observou-se um total de 85 pacientes com relatos de EAs pelo uso de
1. Introduction

Toxoplasmosis is caused by Toxoplasma gondii protozoan (T. gondii), a mandatory intracellular parasite belonging to the phylum Apicomplexa. It is widespread globally and is capable of infecting a wide range of hosts, with felids as the definitive hosts, and humans, birds, and other mammals as intermediate hosts. About a third of the world’s population has a chronic infection, among which seroprevalence varies by country. In Brazil, for example, seroprevalence is higher than 60% (Alday & Doggett, 2017; Dubey et al., 2012).

Most human T. gondii infections occur through ingestion of sporulated oocysts, which are eliminated in feline feces and contaminate soil, water, and food, or through bradyzoites found in the form of tissue cysts in raw or undercooked meat. Tachyzoites are another infectious form. They are present in biological fluids and found during acute infection; they are also responsible for transplacental transmission (Paradynski et al., 2019).

Generally, acute T. gondii infection in immunocompetent individuals is followed by latent infection associated with the formation of cysts in various organs, mainly in the cardiac and skeletal muscles, cerebral parenchyma, and retina. However, latent infection can be reactivated in immunocompromised patients, in whom bradyzoites, a form of latent cyst, are rapidly reversed into replicating tachyzoites, causing severe diseases such as toxoplasmic encephalitis and serious eye injuries (Dunay et al., 2018). Regarding congenital transmission, the consequences of infection can lead not only to outcomes that will accompany the child through life, such as neurological and ocular sequelae, but also cause fetal and perinatal death, which is a public health problem (Serrano, 2016).

There is no treatment to eradicate toxoplasmosis, as the available drugs have no effect on bradyzoite cysts that are...
deposited in the host and can be reactivated later (Bernardo et al., 2015). The only available treatment is for tachyzoites. However, there are considerable variations in drugs, dosage, and treatment duration, and none is considered the gold standard (Wei et al., 2015). In order to suppress tachyzoite replication, most drugs target the inhibition of the enzymes dihydrofolate reductase (DHFR) and dihydropteroate synthase (DHPS) to block the synthesis of folic acid. Thus, it appears that the drugs used in treatments have high rates of cytotoxicity, side effects, and adverse reactions, which often lead to the abandonment of therapy (Alday & Doggett, 2017; Deng et al., 2019).

Thus, the objective of this review is to provide comprehensive information about the profile of adverse events (AEs) caused by the therapy available for the treatment of toxoplasmosis. This entails identifying the drugs and dosages used, and the main clinical reactions.

2. Methodology

This is a qualitative study. Our research was limited to articles written in Portuguese and English, without time restrictions. A bibliographic search of the electronic databases PubMed, SciELO, Cochrane Digital Library, and LILACS was carried out from June to July 2020. The keywords were chosen based on the Health Sciences Descriptors (DeCS) combined with the Boolean operator (AND): toxoplasmosis AND drug therapy AND drug-related side effects and adverse reactions. And the flow diagram that describes the flow of information in the different phases of the review referring to the results of the selection of articles was prepared following the PRISMA parameters.

2.1 Inclusion and exclusion criteria

Original, retrospective, and case reports were included, with the following inclusion criteria: 1) investigation of AEs related to the drugs used in the treatment of toxoplasmosis and 2) studies that provide detailed information about the prevalence of adverse reactions caused by drugs used in toxoplasmosis therapy. The exclusion criteria were: 1) reviews were removed from the literature; 2) studies developed in vitro and in animal models; 3) publications in languages other than Portuguese and English; and 4) lack of adequate data and irrelevant studies regarding not detailed approach to specific adverse events caused by the medication and number of patients.

2.2 Study selection and data extraction

After selecting articles that met the inclusion criteria, two independent reviewers carefully examined their titles, abstracts and full articles for eligibility. Subsequently, reviewer divergences were discussed and resolved by consensus. The extracted information included: year of study and author; adverse events; type of manifestation of toxoplasmosis and the treatment drug.

3. Results and Discussion

The bibliographical research resulted in the selection of 40 articles. Of these, 23 articles were excluded after the reviewers had read the titles and abstracts. Of the 17 articles that were selected for full reading, only 14 articles met all eligibility criteria and were included in this review (Figure 1).
Drugs such as pyrimethamine, sulfadiazine, clindamycin, azithromycin, trimethoprim, sulfamethoxazole (cotrimoxazole), dapsone, spiramicin, and atovaquone can be used to treat toxoplasmosis. However, none of these is satisfactory regarding effectiveness against all forms of *T. gondii* and safety due to the frequent occurrence of adverse events, as demonstrated in 85% of patients treated for ophthalmic toxoplasmosis (Guaraldo *et al.*, 2018; Iaccheri *et al.*, 2008).

Gestational, congenital, cerebral, and ocular toxoplasmosis were observed in case reports and studies published between 1991 and 2018, in which 85 patients were included (Table 1). Eight studies used drugs such as trimethoprim combined with sulfamethoxazole, or a combination of sulfadiazine and pyrimethamine, and reported the concomitant administration of folinic acid, since these drugs inhibit the synthesis of folic acid and are mainly related to AEs associated with bone marrow suppression. However, in four (28.5%) of the 14 studies that used folinic acid, together with the adopted therapy, the patients presented with hematological changes.\(^1,12,14\)
Table 1. Characteristics of studies on adverse reactions caused by drugs used in toxoplasmosis therapy.

| Author                  | Clinical manifestation | No. of Patients | Treatment                                                                 | Adverse Event                                      |
|-------------------------|------------------------|-----------------|---------------------------------------------------------------------------|----------------------------------------------------|
| 1. Canessa et al. (1992)| Cerebral               | 4               | TS 40mg / kg (T 6.6 mg / kg / d + S 33.3 mg / kg / d) + FA (15mg / d)       | Skin and hematological changes                      |
|                         |                        | 1               | TS 120mg / kg (T 20mg / kg + S 100mg / kg / d) + FA (15mg / d)             | Skin changes                                       |
| 2. Cárrion et al. (1999)| Cerebral               | 1               | P (50 mg / d) + S (2g 3x / d)                                             | Stevens-Johnson syndrome                           |
| 3. Caumes et al. (1995) | Cerebral               | 18              | P (AD 100mg + 50mg / d) + S (4g / d)                                      | Skin changes / Stevens-Johnson and Lyell syndromes |
|                         |                        | 15              | P (AD 100mg + 50mg / d) + C (2.4g / d)                                    | Skin changes                                       |
| 4. Marcos et al. (1995) | Cerebral               | 1               | P (75mg / d) + C (600mg / 4x / d)                                         | Skin changes                                       |
| 5. Iaccheri et al. (2008)| Ocular                | 2*              | TS (T 160mg + S 800mg 2x / d)                                             | 2 Skin changes and facial edema                    |
|                         |                        | 3               | A (750mg 4x / d)                                                          | 2 Skin and 1 gastrointestinal change               |
|                         |                        | 9               | S (4g / d)                                                                | Skin changes                                       |
|                         |                        | 13*             | C (300 mg 4x / d)                                                         | 6 Skin and 9 gastrointestinal changes              |
|                         |                        | 4*              | P (AD 100mg + 25mg / d) + AF (15mg 2x / s)                                 | 1 Hematological change, 3 stomachage and 1 headache|
| 6. Kim et al. (2002)    | Ocular                 | 1               | TS (T 160mg / S 800mg / d) + C (600mg 4x / d)                              | Skin and gastrointestinal changes                  |
| 7. Heffenstein et al. (2017)| Ocular      | 9               | P (AD 75mg / 3d + 50mg / d) + S (4g / d) + FA (15mg 2x / s)                | 2 Skin, 2 gastrointestinal and 4 biochemical changes and 1 facial edema |
| 8. McLeod et al. (2006) | Ocular                 | 1               | P + S + FA (DNR)                                                          | DRESS syndrome                                    |
| 9. Yusuf et al. (2013)  | Ocular                 | 1               | P (50mg / d) + S (1g 4x / d) + FA (15mg 2x / s)                            | DRESS syndrome                                    |
| 10. Sousa et al. (2016) | Ocular                | 1               | P (50mg / d) + S (4mg / d) + FA (5mg / d)                                 | DRESS syndrome                                    |
| 11. Nucera et al. (2000)| Gestational            | 1               | TS + E (UD)                                                               | Skin changes                                       |
| 12. Ostlére et al. (1991)| Gestational           | 1               | E (1.5g 2x / d)                                                           | Skin and hematological changes                     |
| 13. Velter et al. (2018)| Gestational            | 1               | P + S (UD)                                                                | Stevens-Johnson syndrome                           |
| 14. Tei et al. (2016)   | Congenital             | 6               | P (3mg / kg 3-9d) + S (25mg / kg 4x / d) + FA (50mg / s 1x / s) for 2m and P (1.25mg / kg 10-10d) + SX (25mg / kg 10-10d) + FA (50mg / s 1x / s) for 10m | Skin and hematological changes                     |

Caption: P (oral Pyrimethamine), S (oral Sulfadiazine), FA (oral Folinic Acid), C (oral Clindamycin), TS (oral Trimethoprim and oral Sulfamethoxazole), E (oral Spiramycin), SX (oral Sulfadoxine), A (Atovaquone orally), d (Day), s (Week), x (Times), m (Months), AD (Attack dose), UD (Unreported dose).

* More than 1 adverse event was reported by the same patient.
'Biochemical changes: increased liver enzymes and creatinine
Source: Authors.
Cutaneous AEs were reported in 13 studies (92.8%), including skin changes, Lyell's syndrome (SL), and Stevens-Johnson syndrome (SJS). The most reported AE was skin changes (57.1%), mainly associated with pyrimethamine treatment, with dosages in the range of 25–150 mg per day. In addition, two studies reported adverse reactions in the gastrointestinal system, and in one of these, vomiting was the most prevalent reaction; however, diarrhea, stomach pain, and gastrointestinal bleeding were observed in another study. Three studies (21.4%) reported the development of SJS using a combination of and sulfadiazine. In one study, eighteen patients (18/85; 21.1%) manifested SL.

Drug reaction with eosinophilia and systemic symptoms (DRESS) was reported in three studies (21.4%), two of which also reported AEs such as liver failure, rash, hematological changes, and biochemical changes. Furthermore, in one of the studies, rash, hematological changes, and persistent lymphadenopathy were reported. Despite the severe symptoms of DRESS syndrome (DS), all affected patients showed improvement in clinical signs after medication replacement and the administration of corticosteroids. The combination of pyrimethamine and sulfadiazine, at different dosages, together with folinic acid, was used to treat ocular toxoplasmosis. However, analysis of the studies concluded that the severe hypersensitivity reaction was due to sulfadiazine.

The profile of AEs associated with treatment using drugs differed according to the clinical manifestations of toxoplasmosis (Table 1). Spiramycin-based therapy was observed in 14.3% of studies on gestational toxoplasmosis with dermatological AEs. One of those 14 studies reported an AE in children with congenital toxoplasmosis, and six patients developed hematological changes such as neutropenia, eosinophilia, and anemia. These changes were considered to be consequences of treatment with a combination of sulfadinoxine and pyrimethamine at doses of 3 mg/kg and 25 mg/kg per day, respectively. Similarly, Ben-Harari et al. (2017) reported AEs associated with bone marrow suppression in children with congenital infection using pyrimethamine and developed hematological modifications such as neutropenia, eosinophilia, thrombocytopenia, and anemia.

Two studies on cerebral toxoplasmosis and two on ocular toxoplasmosis included trimetropime combined with sulfamethoxazole and clindamycin, as well as monotherapy with clindamycin and pyrimethamine, and clindamycin only, administered individually. In one of these studies on ocular toxoplasmosis, the therapy was based on trimetropime combined with sulfametoxazole and clindamycin, with a report of dermatological AEs caused by hypersensitivity to clindamycin treatment. This result corroborates other studies that also reported dermatological AEs due to the use of the trimetropime plus sulfametoxazole with clindamycin at daily dosages varying between 300 mg and 2.4 mg.

The most frequent severe clinical manifestation of T. gondii is encephalitis (cerebral toxoplasmosis), which generally consists of several discrete brain lesions and is more common in immunosuppressed patients. In this study, 40 (47%) of 85 patients with human immunodeficiency virus (HIV) infection developed cerebral toxoplasmosis. This analysis corroborates Vidal (2019), who reported that manifestations in the central nervous system (CNS) stand out among the severe clinical forms of toxoplasmosis, mainly affecting patients with acquired immunodeficiency syndrome (AIDS) due to the use of medications for the treatment of toxoplasmosis.

The combination of sulfadiazine and pyrimethamine is used in toxoplasmosis therapy, but it affects the CNS, as observed in two studies. However, due to adverse reactions, mainly caused by sulfadiazine, these drugs are typically replaced, or the treatment is abandoned. Marcos et al. (1995) highlighted that treatment of toxoplasmic encephalitis in HIV-infected patients occurs continuously throughout life. Thus, due to the remarkable occurrence of hypersensitivity reactions, the therapeutic arsenal has been shown to be insufficient for patients who continually need medications to combat T. gondii.

Thus, it was observed that the combination of pyrimethamine with sulfadiazine and folinic acid is the most used treatment regimen, despite the high risk of toxicity. According to Alday & Doggett (2017), trials that used pyrimethamine with...
sulfadiazine for the treatment of toxoplasma encephalitis led to the discontinuation of therapy in one-third of patients. The study also highlighted that sulfadiazine can be replaced with clindamycin if the patient is allergic to drugs in the sulphonamides class of antibiotics. However, it has been observed that clindamycin is a less effective drug for preventing the recurrence of infection and that it also has similar toxicity rates.

Sulphonamides are often associated with rare and potentially fatal drug hypersensitivity reactions, such as DS. This reaction can cause rash, fever, lymphadenopathy, hematological changes, and affect internal organs (Yusuf et al., 2013; Karakayali et al., 2017). Furthermore, according to Cárrion-Cárrion et al. (1999), SSJ may also be reported after the administration of sulphonamides and is characterized by severe skin rashes (acute epidermal necrosis) and fatal syndrome in about 5% of cases. SL and SJS have different degrees of severity for the same conditions; however, SL is considered to be more severe (Siah et al., 2009).

Regarding the clinical manifestations of toxoplasmosis, it is important to emphasize that toxoplasmosis acquired during pregnancy is another means of transmitting the parasite and has significant relevance because of the risk of vertical transmission and the development of serious damage in the infected child, such as intracranial calcification, eye injury, and microcephaly or anencephaly. The most severe symptoms are observed in babies whose mothers were infected in the third trimester of pregnancy, in addition to abortion, which can also occur during this period (Esperança et al., 2019). Studies have reported that in the case of seropositivity, immediate treatment should be given using spiramycin. However, pyrimethamine, sulfadiazine, and folinic acid are administered in cases of suspected congenital infections. There are risks of adverse teratogenic and hematological effects, in addition to reactions that can also occur in the mother (Bernardo et al., 2015), as in Velter (2018), in which the development of SJS was verified in pregnant women after the administration of a combination of pyrimethamine and sulfadiazine.

Ocular toxoplasmosis also stands out as the most common cause of posterior uveitis, which mainly affects the retina and its underlying layer, causing focal necrotizing retinochoroiditis, which is characterized by pigmented macular lesions with necrotic spots on the retina (Lie et al., 2019). It appears that there are no antiparasitic agents capable of eradicating T. gondii from ocular tissues, and the most commonly used treatment, pyrimethamine plus sulfadiazine and folinic acid, still has questionable efficacy and can often cause more problems than the disease itself, such as provoking DRESS syndrome (Cárrion-Cárrion et al., 1999; Kim et al., 2002; Oliveira, 2012; Schallhorn & Gonzales, 2013; Sousa et al., 2016; Velter et al., 2018).

In this review, the number of studies and the total sample size analyzed for each of the manifestations of toxoplasmosis were low. In addition, the specific dosage, study design, and patient population all differed between studies within a given clinical manifestation. Most treatment regimens involve combinations of drugs, which makes it difficult to analyze each drug’s individual relationship to the reported AEs.

4. Conclusion

In this study, it was found that the profile of AEs associated with toxoplasmosis treatments differed according to the manifestation of toxoplasmosis, and the prevalence of AEs related to hematological changes was mainly in treatments based on pyrimethamine combined with sulfadiazine and trimethoprim combined with sulfamethoxazole. Dermatological changes associated with severe syndromes are often related to the use of pyrimethamine and sulfadiazine, both in ocular and brain toxoplasmosis, respectively. However, in gestational toxoplasmosis, this change is correlated with spiramycin-based therapy. Furthermore, in congenital toxoplasmosis, the most frequent AEs were associated with bone marrow suppression, with the use of pyrimethamine being linked to this change. Hence, the need for randomized clinical trials to compare the efficacy, profile of
AEs, and medication adherence among the various medications used against toxoplasmosis is highlighted in order to establish a gold standard protocol. Considering this scenario, the development of safer, more efficient, and less toxic compounds against *T. gondii* is essential.

**Acknowledgments**

This study was financed in part by the Coordenação de Aperfeiçoamento de Pessoal de Nível Superior - Brasil (CAPES) -Finance Code 001

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