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REVISÃO SISTEMÁTICA DOS EFEITOS ADVERSOS DO TRATAMENTO DA LEISHMANIOSE CUTÂNEA NO NOVO MUNDO

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REVISÃO SISTEMÁTICA DOS EFEITOS ADVERSOS DO TRATAMENTO DA LEISHMANIOSE CUTÂNEA NO NOVO MUNDO

LUIZ FILIPE GONÇALVES DE OLIVEIRA

Dissertação apresentada ao Curso de Pós-Graduação em Pesquisa Clínica em Doenças Infecciosas do Instituto de Pesquisa Clínica Evandro Chagas para obtenção do grau de Mestre em Ciências

Orientadores: Dr. Carlos Augusto Andrade e Dr. Armando de Oliveira Schubach

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Dr. Armando de Oliveira Schubach

Aprovada em / /

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Dra Paula Dadalti Granja

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Intituto ----------

Aos meus amados filhos Juliana e Thiago que são minha inspiração.

A minha dedicada mãe pelo apoio e amor incondicional.

Aos meus queridos avós Altair, Hermínia, Deuse e Edi (*in memorian*) que muito colaboraram com minha educação e caráter.

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Oliveira, LFG. **Revisão Sistemática dos Efeitos Adversos do Tratamento da Leishmaniose Cutânea no Novo Mundo**. Rio de Janeiro, 2010. 39f Dissertação [Mestrado em Pesquisa Clínica em Doenças Infecciosas] - Instituto de Pesquisa Clínica Evandro Chagas.

RESUMO

Introdução: Os antimoniais pentavalentes são os medicamentos de primeira linha para o tratamento da forma cutânea da Leishmaniose Tegumentar Americana. A anfotericina B e a pentamidina são considerados de segunda linha. Embora estes medicamentos sejam usados há décadas, sabe-se pouco sobre sua segurança. Na atual revisão identificamos e classificamos os principais efeitos adversos associados e, quando possível, estimamos as freqüências. **Métodos**: Estudos de intervenção, séries e relatos de caso contendo registro dos efeitos adversos clínicos, laboratoriais ou eletrocardiográficos foram pesquisados sistematicamente em 10 bases de dados eletrônicas, entre 13 de agosto de 2.008 e 31 de março de 2009. **Resultados**: Nos 65 estudos incluídos, foram tratados um total de 4.359 pacientes de 12 países, infectados por oito diferentes espécies de *Leishmania*. Apesar do pequeno número de medicamentos utilizados nos artigos incluídos nesta revisão, encontramos grande variabilidade de esquemas terapêuticos. Consequentemente, foi necessário agrupar por aparelhos e sistemas os efeitos adversos dos antimoniais pentavalentes e da pentamidina, independente da formulação, dose diária, tempo de tratamento e via de administração. As frequências de efeitos adversos foram calculadas com base nas informações de 32 artigos envolvendo 1866 pacientes. Os efeitos adversos clínicos mais freqüentemente relatados com os antimoniais pentavalentes e pentamidina foram: dores músculo-esqueléticas, alterações gastrointestinais e cefaléia leves a moderadas. Com os antimoniais pentavalentes também foram observados prolongamento do intervalo QTc do eletrocardiograma e elevação leve a moderada das enzimas hepáticas e pancreáticas. **Conclusão:** Os antimoniais pentavalentes foram os medicamentos mais utilizados (66,5%), seguidos da pentamidina (29,6%). Tanto o tratamento com os antimoniais como com a pentamidina exibiu altas freqüências de efeitos adversos leves a moderados. Concluímos pela necessidade do desenvolvimento de novos fármacos mais seguros para o tratamento da leishmaniose cutânea e aplicação de critérios definidos na coleta de informação de efeitos adversos em estudos observacionais. Além disso, a realização de ensaios clínicos com monitoramento de efeitos adversos clínicos, laboratoriais e eletrocardiográficos, com critérios de classificação de gravidade, independente do esquema terapêutico adotado.

Palavras-chave: Revisão Sistemática; leishmaniose cutânea/tratamento; agentes antiprotozoários /efeitos adversos

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ABSTRACT

Introduction: Pentavalent antimonials are first line drugs for treatment of cutaneous leishmaniasis. Amphotericin B and pentamidine are considered second line drugs. Although these drugs are used for many years, little is known about their safety. In this review we identified and classified the main adverse effects associated with drug therapy and when it was possible their frequencies were calculated. **Methods**: Systematic searches were conducted in the medical literature using 10 database between August 13th 2008 and March 31th 2009. Clinical trials and observational studies were included since they reported subjective complaints or laboratory and electrocardiographic abnormalities. **Results**: Sixty-five articles were included in which were treated 4,359 patients from 12 countries, infected with eight different species of *Leishmania*. Even though the small number of drugs used in the articles included in this review, we find a great variety of treatment regimens. Thus, it was necessary to group the adverse effects of pentavalent antimonials and pentamidine by physiological systems regardless of formulation, daily dose, treatment time and route of administration. Frequencies of adverse effects were calculated based on data from 32 articles involving 1,866 patients. Mild to moderate musculoskeletal pain, gastrointestinal disorders and headache were the most common subjective complaints reported with pentavalent antimonials and pentamidine therapy. Prolongation of the corrected QT interval and mild to moderate elevated liver and pancreatic enzymes were related with pentavalent antimonials treatment. **Conclusion**: Pentavalent antimonials and pentamidine were most used drugs (66.5% and 29.6%, respectively). Both drugs demonstrated high frequency of mild to moderate adverse effects. The development of new safety drugs is need. More clinical trials and observational studies should be conducted to determine the best therapeutical regimens including monitoring for adverse effects, with well defined criteria of severity.

Key-words: Systematic Review, cutaneous leishmaniasis / drug therapy; antiprotozoal agents / adverse effects

SUMÁRIO

1. INTRODUÇÃO

1.1 Leishmaniose cutânea

As leishmanioses são um grupo de doenças causadas por diversas espécies de protozoários do gênero *Leishmania* e transmitidas através da picada de insetos de diferentes espécies de flebotomíneos.[1] Os parasitas são capazes de produzir alterações na pele, mucosas e cartilagens, caracterizando a forma tegumentar da doença.[2]

As leismanioses causadas por espécies dermotrópicas são encontradas em 88 países no mundo e são endêmicas em 82 destes. A Organização Mundial de Saúde estima que a incidência anual da doença seja de cerca de 1,5 milhões de casos novos/ano. O Brasil, juntamente com outros seis países em desenvolvimento (Afeganistão, Argélia, Irã, Peru, Arábia Saudita e Síria) concentra cerca de 90% dos casos de leishmaniose cutânea.[3] A infecção não está restrita às áreas remotas e a urbanização da doença é um fato que ocorre em diversos países, inclusive o Brasil.[4]

A leishmaniose tegumentar americana pode apresentar-se clinicamente de duas formas no ser humano. Na forma cutânea (leishmaniose cutânea), as lesões podem manifestar-se de maneira localizada ou disseminada. A forma mucosa (leishmaniose mucosa), causada por *L. brazilensis*, caracteriza-se por lesões destrutivas localizadas nas vias aéreas superiores.[4,5]

Os antimoniais trivalentes, conhecidos como tártaros eméticos foram introduzidos na terapêutica por Gaspar de Oliveira Vianna em 1912, quando o médico brasileiro tratava pacientes com leishmaniose cutânea. Alguns anos depois, na Itália, este composto foi utilizado no tratamento do calazar. Devido à toxicidade elevada e os graves efeitos colaterais associados ao tártaro emético, formulações contendo antimônio pentavalente foram desenvolvidos.[6] Atualmente, estes fármacos são considerados pela Organização Mundial da Saúde como primeira linha para o tratamento da leishmaniose cutânea, por apresentam melhor índice terapêutico do que as chamadas drogas de segunda linha, como a anfotericina B e a pentamidina. Índice terapêutico é uma medida utilizada em Farmacologia que relaciona a dose necessária para produzir efeito terapêutico com a dose responsável pelo surgimento de efeitos tóxicos. Quanto menor for este índice mais facilmente o fármaco atingirá níveis plasmáticos

tóxicos.[7] Como as últimas apresentam maior risco de toxicidade, são recomendadas apenas nos casos onde há contra-indicação, intolerância ou resistência aos antimoniais.[8,9]

No Brasil, o tratamento da leishmaniose cutânea é realizado quase exclusivamente com um determinado tipo de antimonial pentavalente, o antimoniato meglumina (Glucantime®). Porém, devido às diferenças regionais de sensibilidade dos parasitos a este medicamento, as dosagens devem ser ajustadas de acordo com o padrão da resposta terapêutica observada, definida pelos critérios de cura.[10,11]

Além disso, existem ainda esquemas alternativos para utilização dos antimoniais pentavalentes, como sua administração intralesional, o emprego de baixas doses (abaixo de 10mg/Kg/dia) e combinação com outros medicamentos como imiquimode, alopurinol e imunoterapia.[12,13,14] Há ainda, uma variedade de tratamentos tópicos empregados para leishmaniose cutânea, tais como: aplicação de calor no local da lesão, nitrogênio líquido, sulfato de zinco, laser, remoção cirúrgica. Contudo, apesar da maioria destas modalidades terem sido testadas mundialmente em vários estudos clínicos, os resultados são controversos.[15]

1.2 Efeitos adversos: definição e terminologia

Embora os medicamentos recomendados para o tratamento da leishmaniose cutânea sejam usados há décadas, conhece-se pouco sobre sua segurança. A segurança de um fármaco está relacionada à incidência e a gravidade de eventos que, de alguma forma, interferem no alcance dos objetivos terapêuticos.[16] Estes eventos são frequentemente denominados "problemas relacionados com medicamentos", termo traduzido do inglês *drug-related problems* ou *adverse drugs events*. Estes são problemas de saúde, entendidos como resultados clínicos negativos, derivados da farmacoterapia que não conduzem ao alcance do objetivo terapêutico ou levam ao surgimento de efeitos não desejados. A definição para o termo é ampla e inclui problemas como falha terapêutica, intoxicação acidental ou intencional, uso abusivo de drogas, erros de administração e problemas de adesão.

"Efeitos adversos a medicamentos" são eventos desfavoráveis associados temporalmente ao seu uso, com provável relação causal.[17] De acordo com Capellá e Laporte, os termos "reação adversa", "efeito indesejável" e "doença iatrogênica" são equivalentes e correspondem ao conceito anterior.[18] No entanto, vários outros termos podem ser encontrados na literatura internacional, causando grande confusão. O Quadro 1, mostra os principais

termos relacionados à efeitos adversos a medicamentos utilizados nas bases MedLine e *Excerpta Medica* (*Embase*).[19]

MEDLINE	*EMBASE*
Poisoning	*Side effect*
Toxicity	*Adverse drug reaction*
Chemically induced	*Drug toxicity*
Contraindications	*Complications*
Complications	

Quadro 1: Termos indexados nas principais bases eletrônicas.
Adaptado de Locke et al (2007).[19]
Embase: *Excerpta Medica*

Estudos clínicos em seres humanos devem seguir as normas de boas práticas clínicas e, obrigatoriamente, relatar todas as reações adversas, inclusive os estudos não intervencionais.[20] A diretriz E2A do *International Conference on Harmonisation* define e regulamenta os estudos de segurança farmacológica.[21] Este guia aplica-se a estudos que envolvam novos medicamentos e produtos derivados da biotecnologia para uso em humanos, além de medicamentos já aprovados.

1.3 Revisões Sistemáticas

Existe um interesse mundial no desenvolvimento de medidas que garantam que as políticas públicas e tomadas de decisão sejam baseadas nos resultados de pesquisas relevantes e confiáveis.[22]

Revisões bibliográficas narrativas são resumos da literatura especializada sobre um determinado tema. Nestas revisões, muitas vezes os dados analisados são interpretados de forma inadequada, fornecendo conclusões espúrias ou pouco claras.[23,24]

Uma Revisão sistemática compreende uma pesquisa ampla e criteriosa de estudos primários focados em uma determinada questão clínica. Os critérios de seleção dos artigos são claros e os critérios de elegibilidade reprodutíveis. Existe análise crítica dos estudos quanto à sua qualidade e síntese dos resultados de acordo com métodos explícitos e pré-determinados. Se os dados obtidos preencherem certos critérios, como por exemplo, homogeneidade, podem ser combinados em uma meta-análise.[25]

Revisões sistemáticas são componentes importantes da "medicina baseada em evidências", porém a maioria dos revisores concentra-se na determinação da efetividade do

tratamento ou intervenção. Este foco no benefício da terapêutica aliada à omissão de informações sobre os efeitos adversos pode trazer uma estimativa superestimada sobre a efetividade do tratamento.[19]

2. JUSTIFICATIVA

Encontramos na literatura apenas duas revisões sistemáticas para o tratamento da forma cutânea da leishmaniose tegumentar no Novo Mundo. Na primeira, publicada por Tuon *et al*, foram incluídos alguns ensaios não controlados e outros com pequeno número de pacientes. Este fato acarretou alto grau de heterogeneidade entre os estudos que não foi considerada pelos autores na análise dos dados.[26] Na mais recente, González *et al* incluíram 38 ensaios clínicos randomizados abordando vários esquemas terapêuticos, envolvendo principalmente infecções por *L. braziliensis* e *L. panamensis*.[27] Ambas concluíram que não há ainda consenso sobre qual melhor regime de tratamento. Além disso, nenhuma abordou os aspectos relacionados à segurança dos medicamentos utilizados no tratamento da doença.

Assim, a elaboração de uma revisão sistemática que contemple informações sobre a segurança dos vários esquemas terapêuticos, contribui para o estabelecimento do padrão de efeitos adversos clínicos, laboratoriais e eletrocardiográficos para os diferentes fármacos utilizados no tratamento da leishmaniose cutânea no Novo Mundo.

3. OBJETIVOS

3.1 Geral:

Estabelecer o perfil de efeitos adversos associados aos medicamentos recomendados para o tratamento da leishmaniose cutânea no Novo Mundo.

3.2 Específicos:

1- Identificar os efeitos adversos clínicos, laboratoriais e eletrocardiográficos associados a cada medicamento avaliado;
2- Classificar tais efeitos quanto à gravidade;
3- Quando possível, estimar suas freqüências;

4. ARTIGO

O artigo: **"Revisão Sistemática dos Efeitos Adversos do Tratamento da Leishmaniose Cutânea no Novo Mundo"**, autoria de Luiz Filipe Gonçalves de Oliveira, Armando de Oliveira Schubach, Maria de Fátima Martins Moreira, Sônia Regina Lambert Passos, Raquel de Vasconcellos Carvalhaes de Oliveira, Mauro Célio Marzochi e Carlos Augusto Ferreira de Andrade, submetido ao periódico *The Lancet Infectious Diseases*, substitui as seções "Métodos", "Resultados" e "Discussão" da presente dissertação de mestrado.

Systematic Review of the Adverse Effects of Cutaneous Leishmaniasis Treatment in the New World

Abstract

Pentavalent antimonials are first-line drugs for the treatment of the cutaneous form of American tegumentary leishmaniasis. Second-line drugs include amphotericin B and pentamidine. Although these drugs have been used for decades, little is known about their safety. The objective of this review was to identify and classify the main adverse effects associated with these drugs and to estimate the frequency of these effects, whenever possible. Intervention studies, case series and case reports containing information regarding clinical, laboratory or electrocardiographic adverse effects of drugs used for the treatment of cutaneous leishmaniasis were systematically retrieved from 10 databases searched between August 13, 2008 and March 31, 2009. The 65 studies included in this review had treated a total of 4,359 patients from 12 countries infected with eight different *Leishmania* species. Despite the small number of drugs used in these studies, a wide variability in the therapeutic regimens was observed. As a consequence, the adverse effects of pentavalent antimonials and pentamidine needed to be classified jointly according to system, irrespective of formulation, daily dose, duration of treatment and route of administration. The frequencies of adverse effects were calculated based on the data of 32 articles involving 1,866 patients. The most frequently reported clinical adverse effects of pentavalent antimonials and pentamidine were musculoskeletal pain, gastrointestinal disturbances, and mild to moderate headache. Electrocardiographic QTc interval prolongation and a mild to moderate increase in liver and pancreatic enzymes were additional adverse effects of pentavalent antimonials. In conclusion, clinical trials are necessary to monitor the clinical, laboratory and electrocardiographic adverse effects using criteria for the classification of severity.

Key-words: systematic review, cutaneous leishmaniasis/treatment; antiprotozoal agents/adverse effects.

Introduction

Leishmaniases are parasitic diseases caused by different protozoan species of the genus *Leishmania*, including those of the subgenus *Leishmania*, which display dermotropism or viscerotropism (Old and New World), and of the subgenus *Viannia*, which are exclusively dermotropic (New World). The parasites are transmitted by the bite of different sandfly species.[1] Leishmaniases caused by dermotropic species are endemic in 82 countries, with an incidence of approximately 1.5 million cases per year. About 90% of cutaneous leishmaniasis cases are concentrated in Brazil and six other developing countries.[2] American tegumentary leishmaniasis, a term comprising cutaneous forms with a potential to evolve to secondary mucosal forms, is mainly caused by *Leishmania (Viannia) braziliensis* and is endemic in various regions of the Americas.[3-5]

Pentavalent antimonials are the first-line drugs for the treatment of the cutaneous form of leishmaniasis in the New World. The recommended dose range is 10 to 20 mg Sb^{5+}/kg/day for a minimum period of 20 days.[5,6,7,8] Other therapeutic regimens are also used, but no consensus exists over which is the best one.[9,10] In view of their higher toxicity, amphotericin B and pentamidine are second-line drugs, which are recommended in cases of contraindication, intolerance or resistance to antimonials.[8,11] The efficacy of different drugs seems to vary according to the *Leishmania* species involved.[12]

Adverse drug effects are unfavorable events associated in time with the use of a medication and may have a causal relationship.[13] The safety of a drug is related to morbidity and mortality resulting from the incidence and severity of adverse effects.[14] Although the drugs recommended for the treatment of cutaneous leishmaniasis have been used for decades, little is known about their safety.

Systematic reviews give priority to efficacy over safety.[15] We found only two systematic reviews on the treatment of cutaneous leishmaniasis in the New World, but none of them considered safety-related issues.[9,10]

The objective of the present systematic review was to identify and classify the main clinical, laboratory and electrocardiographic adverse effects associated with drugs recommended for the treatment of the cutaneous form of leishmaniasis in the New World, and to estimate the frequency of these adverse effects.

Methods

The present systematic review was conducted according to the PRISMA guideline (Preferred Reporting Items for Systematic Reviews and Meta-Analyses).[16]

Search strategies and selection criteria

The searches and review process were performed according to a pre-established protocol restricted to the cutaneous form of leishmaniasis in the New World. Intervention studies, case series and case reports, in which patients were treated with the recommended drugs and clinical, laboratory or electrocardiographic adverse effects were recorded, were included. In the case of experimental drug studies in which the control group received the approved drugs, only this group was evaluated. Studies using miltefosine were included since this drug is currently under evaluation for the treatment of cutaneous leishmaniasis in the New World. There were no restrictions in terms of patient age or language of the published articles.

The following scientifically reliable databases providing electronic access to bibliographic references were chosen: PubMed, Literatura Latino-Americana e do Caribe em Ciências da Saúde (LILACS), Cochrane, Scopus, Web of Science, Science Direct, Excerpta Medica Database (Embase), Scielo, Highwirepress, and Scirus. Search strategies combining the following keywords were elaborated for each database: adverse effects, adverse drug

reaction and side effects, preceded by the names of the drugs selected (antimony, sodium stibogluconate, meglumine antimoniate, pentamidine isethionate, pentamidine mesylate, amphotericin B, miltefosine), and treatment, drug therapy, leishmaniasis, cutaneous. The Scirus database also covered grey literature. The complete search strategies are summarized in Appendix 1. The searches were started on August 13, 2008 and were updated until March 31, 2009. The reference lists of all articles were reviewed manually for the identification of new articles.

A database of the electronic search results was created with the EndNote X1 program. Duplicate citations were eliminated. Potentially relevant titles and abstracts were independently selected by the pairs of reviewers LFGO/CAFA and LFGO/AOS. Divergences were resolved by consensus or by a third reviewer, if necessary.

Data extraction

The quality of the studies initially selected was evaluated independently by the same pairs of reviewers. Studies in which the monitoring of clinical, laboratory or electrocardiographic adverse effects was described in the methods section were considered to be adequate. Independent data extraction was performed by filling out a standard form (Appendix 2). During this step, divergences were also resolved by consensus or by a third reviewer, if necessary. The severity of adverse effects was classified according to the criteria adopted by the Acquired Immunodeficiency Syndrome Clinical Trials Group.[17] The articles approved were classified according to the type of study, country of contraction of the infection, and therapeutic regimen. A list of adverse effects was obtained and frequencies were calculated, whenever possible.

Results

The search of the 10 databases initially yielded 1,358 abstracts; 86 of them were selected for complete reading of the articles. In addition, 36 articles were obtained by cross-

referencing, resulting in 122 studies. Of these, the following 65 studies were approved and included in the systematic review: 31 clinical trials, 28 case series, and six case reports (Figure 1).

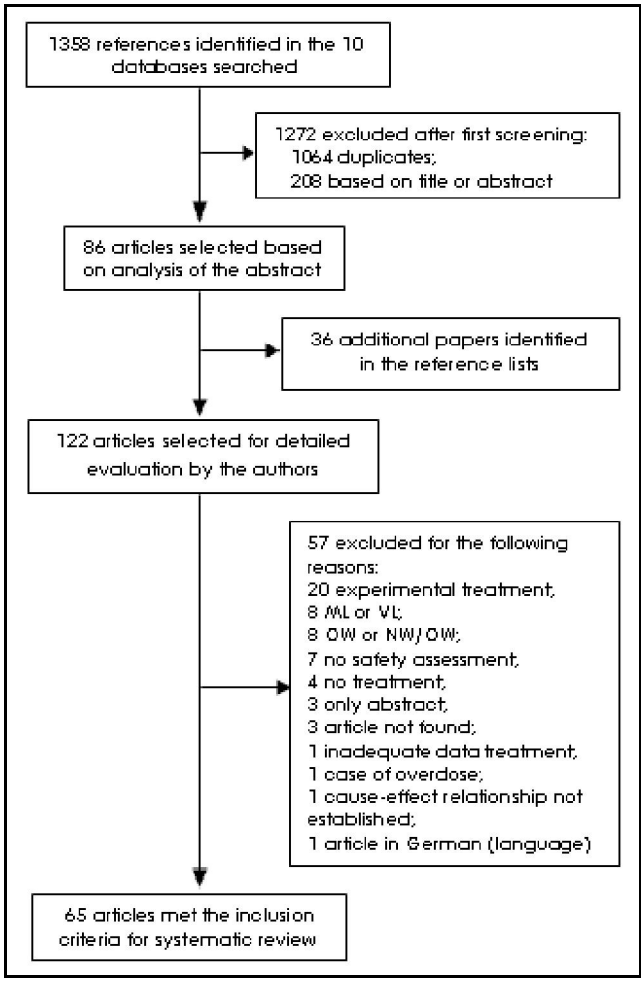

Figure 1: Flow chart illustrating the selection process of the studies. ML: mucosal leishmaniasis; VL: visceral leishmaniasis; OW: Old World; NW: New

The 65 studies included had treated a total of 4,359 patients who contracted the infection in the following countries: Brazil, Colombia, Panama, Bolivia, Guatemala, French Guiana, Peru, Venezuela, Ecuador, Mexico, and Argentina. The *Leishmania* species involved were: *L. (Viannia) braziliensis*, *L. (V.) guyanensis*, *L. (V.) panamensis*, *L. (V.) naiffi*, *L. (V.) shawi*, *L. (Leishmania) mexicana*, *L. (L.) amazonensis*, and *L. (L.) chagasi*.

Table 1 shows the general characteristics of each study and the respective therapeutic regimen used.

Table 1: Studies providing information about the adverse effects of cutaneous leishmaniasis treatment in the New World.

First author, year	Country	N	Drug	Therapeutic regimen
		CLINICAL TRIALS		
Andersen, 2005[61*]	Peru	40	MA	20 mg/kg/day, 20x, continuous IV
		40	PI	2 mg/kg/day, 7x, alternate days
De Paula, 2003[42*]	Brazil	41	MA	20 mg/kg/day, 20x, continuous IV
		38	PI	4 mg/kg/day, 3x, alternate days
Correia, 1996[67*]	Brazil	16	MA	10 mg/kg/day, 20x, continuous IM
		15	PI	4 mg/kg/day, 8x, alternate days
Soto, 1993[63*]	Colombia	23	MA	20 mg/kg/day, 20x, continuous IM
		27	PI	2 mg/kg/day, 7x, alternate days
Wortman, 2002[33*]	Panama	19	SSG	20 mg/kg/day, 20x, continuous IV
		19		20 mg/kg/day, 10x, continuous IV
Ballow, 1987[68*]	Panama	19	SSG	20 mg/kg/day, 20x, continuous IV
		21		10 mg/kg/day, 20x, continuous IV
		12		
Oster, 1985[25]	NS	12	SSG	600 mg/day, 10x, continuous IV
		12		
Palacios, 2001[69]	Colombia	68	MA	20 mg/kg/day, 20x, continuous IM
		68		20 mg/kg/day,10x, continuous IM
Oliveira-Neto, 1997[19*]	Brazil	12	MA	5 mg/kg/day, 30x, continuous IV
		11		20 mg/kg/day, 30x, continuous IV
Arana, 1994[31*]	Guatemala	22	MA	20 mg/kg/day, 20x, continuous IV
		22		20 mg/kg/day, 10x,continuous IV
Kopke, 1991[20]	Brazil	14	MA	14 mg/kg/day, 20x, intermittent IV
		12		28 mg/kg/day, 10x, intermittent IV
Deps, 2000[38]	Brazil	32	MA	15 mg/kg/day, 20x, continuous IM
		31	SSG BP88	
Saldanha, 2000[34*]	Brazil	47	MA	20 mg/kg/day, 20x, continuous IV
		64	SSG BP88	
Saldanha, 1999[44*]	Brazil	58	MA	20 mg/kg/day, 20x, continuous IM/IV
		69	SSG BP88	-
Saènz, 1987[70*]	Panama	29	MA	20 mg/kg/day, 20x, continuous IM
		30	SSG	
	Bol/Col	20/30	MA	20 mg/kg/day, 20x, continuous IM
Soto, 2004[36*]	Bol/Col	8/8	SSG	20 mg/kg/day, 20x, continuous IM
	Bol/Col	17/31	SSG BP88	20 mg/kg/day, 20x, continuous IM
Soto, 1994[57*]	Colombia	38	PI	2 mg/kg/day, 4x, alternate days
		56		3 mg/kg/day, 4x, alternate days

		16		50 mg/day, 20x
Soto, 2001[66*]	Colombia	19	MT	50 mg/day, 7x + 100 mg/day, 13x
		17		100 mg/day, 7x + 150 mg/day, 13x
		20		150 mg/day,28x
Soto, 2004[65*]	Colombia	49	MT	50 mg/day, 28x
	Guatemala	40		50 mg/day, 28x
CONTROL GROUPS OF EXPERIMENTAL DRUG STUDIES				
Krolewiecki, 2007[30*]	Argentina	23	MA	10 mg/kg/day, 28x, continuous IM
Arevalo, 2007[71]	Peru	7	MA	20 mg/kg/day, 20x, continuous IV
Armijos, 2004[72*]	Ecuador	36	MA	20 mg/kg/day, 10x, continuous IM
Velez, 1997[73]	Colombia	67	MA	20 mg/kg/day, 20x, continuous IM
Martinez, 1997[35*]	Colombia	49	SSG	20 mg/kg/day, 15x, continuous
Hepburn, 1994[74]	Belize	7	SSG	20 mg/kg/day, 20x, continuous IV
Hepburn, 1994[43*]	Belize	17	SSG	20 mg/kg/day, 20x, continuous IV
Martinez, 1992[75]	Colombia	33	SSG	20 mg/kg/day, 15x, NS
Navin, 1992[32*]	Guatemala	40	SSG	20 mg/kg/day, 20x, continuous IV
Navin, 1990[23*]	Guatemala	22	MA	850 mg/day, 15x, continuous IM
Saenz, 1990[76*]	Panama	19	SSG	20 mg/kg/day, 20x, continuous IM
Convit, 1987[45*]	Venezuela	42	MA	17 mg/kg/day, 20x, intermittent IM
CASE SERIES				
Oliveira-Neto, 2006[21*]	Brazil	40	MA	405 mg/day, alternate days, IM
Name, 2005[41]	Brazil	183	MA	20 mg/kg/day, 20x continuous NS
Romero, 2003[77*]	Brazil	73	MA	20 mg/kg/day, 20x, continuous, IV
Passos, 2001[27]	Brazil	358	MA	15 mg/kg/day, 10 days intermittent, IM
Romero, 2001[78]	Brazil	118	MA	20 mg/kg/day, 20x, continuous, IV/IM
Ribeiro, 1999[79*]	Brazil	62	MA	15 mg/kg/day, 10x, intermittent NS
Oliveira-Neto, 1997[18*]	Brazil	159	MA	5 mg/kg/day, 30x, continuous IM
Chulay, 1988[24*]	Panama/Colombia	3	MA	850 mg/day, 20x, continuous IM
Lawn, 2006[80*]	NS	60	SSG	20 mg/kg/day, 21x, continuous NS
Name, 2005[41]	Brazil	34	SSG	20 mg/kg/day, 20x, continuous NS
Scope, 2003[37*]	Bolivia	12	SSG	600 mg/day, 2x + 20mg/kg/day, 19x
Seaton, 1999[28*]	Belize	13	SSG	20 mg/kg/day, 20x, continuous IV
Zlotogorski, 1998[39*]	Bolivia/Peru	8	SSG	20 mg/kg/day, 18x, continuous IV
Wortmann, 1998[29*]	Panama	90	SSG	20 mg/kg/day, 10x, intermittent NS
Gasser, 1994[40*]	Peru	10	SSG	20 mg/kg/day, 20x, continuous IV
Hepburn, 1994[81*]	Belize	12	SSG	20 mg/kg/day, 20x, continuous IV
Hepburn,1993[22*]	Belize	101	SSG	600-800 mg/day, 10x, intermittent IV
	Belize	72	SSG	1200 mg/day, 14x, intermittent IV
Chulay, 1988[24]	Panama/Colombia	20[a]	SSG	10 mg/kg/day, 10x, intermittent NS
Henderson, 1985[26]	NS	22	SSG	600 mg/day, 10x, continuous NS
Oliveira-Neto, 1997[51*]	Brazil	74	MA	NS, IL

Barrios, 1986[53*]	Brazil	6	MA	1 ampule, 2x, IL
Gadelha, 1990[52*]	Brazil	64	MA	1-10 mL, 1x/week; then 1x/10 or 15
Roussel, 2006[54*]	French Guiana	281	PI	4 mg/kg/day, 4x, alternate days
		137		7 mg/kg single dose
Robledo, 2006[55*]	Colombia	63	PI	4 mg/kg/day, 4x, alternate days
Delobel, 2003[60*]	French Guiana	26[b]	PI	7 mg/kg single dose
Lai A Fat, 2002[62]	French Guiana	235	PM	120 mg/day, 7 a 10x
		80	PI	300 mg/week + 1x or 2x
Nacher, 2001[56*]	French Guiana	198	PI	4 mg/kg/day, 2x, 48-h interval
		12		4 mg/kg/day, 3x, 48-h interval
Dimer-David, 1992[58]	Bolivia	15	PI	4 mg/kg/day, 4x, 48-h interval
		11		4 mg/kg/day, 5x, 48-h interval
Talhari, 1985[59]	Brazil	6	PI	4 mg/kg/day, 3x, 48-h interval
		13		4 mg/kg/day, 4 to 9x, 48-h interval
Solomon, 2007[64*]	Bolivia	7	LAB	3 mg/kg, 6x (total dose 18 mg/kg)
CASE REPORTS				
Oliveira-Neto, 2004[47]	Brazil		MA	5 mg/kg/day, 30x, continuous
Oliveira-Neto, 2004[47]	Brazil		MA	850 mg/day, 30x, continuous
Costa, 2003[50]	Brazil		SSG	10 mg/kg/day, 20x, continuous
Rodrigues, 1999[49]	Brazil		MA	8.1 mg/kg/day, 20x, continuous
Hepburn, 1993[46]	Belize		SSG	20 mg/kg/day, 20x, continuous
Kopke, 1993[48]	Brazil		MA	20 mg/kg/day, 30x, continuous
Koerber,1978[82]	Mexico		SSG	600 mg/day, 10x, continuous

MA: meglumine antimoniate; PI: pentamidine isethionate; SSG: sodium stibogluconate; SSG BP88: sodium stibogluconate (Shandong Xinhua Pharmaceutical Co.); MT: miltefosine; PM: pentamidine mesylate; LAB: liposomal amphotericin B; NS: not specified; IL: intralesional; IV: intravenous; IM: intramuscular.

* Articles that reported the frequency of one or more adverse effects.

[a] Number of patients evaluated in the study (N = 56).

[b] Number of patients evaluated in the study (N = 45).

Pentavalent antimonials

A total of 2,900 patients received treatment with pentavalent antimonials. Of these, 937 participated in clinical trials, 1,594 in case series, seven were case reports, and 362 corresponded to the control groups of experimental drug studies. Doses below and above the

recommended range (10-20 mg Sb^{5+}/kg/day) were employed in the different therapeutic regimens.[18-20] Some authors adopted fixed doses, irrespective of body weight.[21-26] However, 77.8% of the studies used the maximum dose recommended (20 mg Sb^{5+}/kg/day).

The most frequently reported clinical adverse effects were musculoskeletal pain, nausea, vomiting, diarrhea, abdominal pain, headache, anorexia, asthenia, fatigue, fever, exanthema, erythema, and urticaria (Table 2). Herpes zoster was a complication cited by other authors.[19,20,27-29] Intramuscular administration was associated with mild to moderate pain at the site of application. In some cases, local pain was intense and required the interruption of treatment or change of the route of administration.[30] The most frequently reported local reactions in the case of intravenous administration were thrombophlebitis, phlebitis, and edema.[22,24,25,31,32] Pancreatitis and hepatitis were rarely cited and were related to treatment with 20 mg Sb^{5+}/kg/day for more than 10 days.[33-35]

The most frequently cited laboratory adverse effects were a mild to moderate increase in liver and pancreatic enzymes (Table 3). However, treatment interruption was necessary on some occasions.[28,36- 40] Other adverse effects included elevated creatine phosphokinase and alkaline phosphatase levels, impaired renal function, eosinophilia, leukopenia, and thrombocytopenia.[37,41,42] All of these alterations were transient and returned to normal after the end of treatment, except for two occasions when thrombocytopenia resulted in treatment interruption.[28,43]

The most frequently cited electrocardiographic abnormalities were QTc interval prolongation and ventricular repolarization disturbances (Table 3). Severe arrhythmias were reported in two studies.[44,45]

Rare but severe adverse effects were cited in the case reports and generally occurred after the 15th day of treatment: thrombocytopenia and eosinophilic panniculitis.[46,47] Three cases of death were also reported: the first was due to renal and hepatic insufficiency and

occurred 3 days after the end of treatment with meglumine antimoniate at a dose of 20 mg Sb^{5+}/kg/day for 30 days.[48] The second case of death was due to acute tubular necrosis and occurred on day 20 of treatment with meglumine antimoniate at a dose of less than 10 mg Sb^{5+}/kg/day.[49] The third case was due to cardiorespiratory insufficiency and occurred on day 12 of treatment with sodium stibogluconate BP88 (Shandong Xinhua Pharmaceutical Co.) at a dose of 10 mg Sb^{5+}/kg/day.[50]

Intralesional treatment was reported in three studies (144 patients).[51-53] Mild to moderate adverse effects were reported in about 98% of cases: pain, erythema or edema at the site of application. Urticaria, hemorrhage, lipothymia, and the formation of a local abscess were rarely observed.

Pentamidine

A total of 1,291 patients were treated with pentamidine. Generally, a dose of 2 to 4 mg/kg/day was administered on alternate days, with two to four applications.[54-59] Some authors preferred the administration of a single dose of 7 mg/kg.[54,60]

The most frequently reported clinical adverse effects were musculoskeletal pain, anorexia, abdominal pain, nausea, vomiting, headache, asthenia, and fatigue (Table 2). Mild to moderate pain at the site of application was reported at a frequency higher than 20%. Alterations in the sense of taste such as metallic or bitter taste and hypotension were also observed. [56-58,61-63] Delobel *et al*,[60] using a single dose of 7 mg/kg in a series of 26 cases, observed rhabdomyolysis in 23 patients. The laboratory adverse effects of pentamidine are shown in Table 3. Two reports of hypoglycemia, one of them severe, were found.[57,63]

The frequencies of adverse effects were calculated for pentavalent antimonials and pentamidine based on the information of 32 articles involving 1,866 patients, irrespective of formulation, dose, duration of treatment, or route of administration (Table 4).

Table 2: Number of articles reporting clinical adverse effects according to drug used for the treatment of cutaneus leishmaniasis in the New World.

Clinical adverse effects	MA N=28	SSG N=21	SSG BP88 N=3	PI N=12
	%	%	%	%
Myalgia/arthralgia	78.6	62.0	66.7	58.3
Gastrointestinal disturbances	71.4	52.4	33.3	83.3
Headache	50.0	47.6	66.7	50.0
Anorexia	39.3	23.8	66.7	16.7
Asthenia/fatigue	39.3	14.3	33.3	41.7
Fever	32.1	14.3	66.7	16.7
Cutaneous reactions	28.6	19.0	66.7	8.3
Cardiovascular alterations	17.8	9.5	66.7	25.0
Local pain	14.3	9.5	-	66.7
Taste alterations	10.7	4.8	33.3	25.0
Respiratory alterations	10.7	-	-	8.3
Balance disturbances	10.7	-	-	25.0
Neurological alterations	7.1	14.3	-	25.0
Itching	7.1	9.5	-	-
Pancreatitis	3.6	4.8	33.3	-
Thrombophlebitis	3.6	19.0	-	-
Behavioral alterations	3.6	-	-	8.3
Local reaction	-	14.3	-	8.3
Rhabdomyolysis	-	-	-	8.3

N: Number of articles evaluated (case series, clinical trials and control groups of experimental interventions); MA: meglumine antimoniate; SSG: sodium stibogluconate; SSG BP88: sodium stibogluconate, Chinese fabrication (Shandong Xinhua Pharmaceutical Co.); PI: pentamidine isethionate.

[a] Only one case series used pentamidine mesylate.

Table 3: Number of articles reporting laboratory and electrocardiographic adverse effects according to drug used for the treatment of cutaneus leishmaniasis in the New World.

Laboratory and electrocardiographic adverse effects	MA N=28	SSG N=21	SSG BP88 N=3	PI[a] N=12
	%	%	%	%
↑AST/ALT	39.3	57.1	66.7	8.3
↑Lipase/amylase	14.3	28.6	66.7	-
↑Creatine phosphokinase	7.1	9.5	-	16.7
↑Alkaline phosphatase	3.6	4.8	33.3	-
Eosinophilia	7.1	9.5	-	-
Thrombocytopenia	-	14.3	-	-

Leukopenia	-	9.5	-	-
Hypoglycemia	-	-	-	16.7
Renal alterations	-	4.8	-	-
QTc prolongation	17.8	14.3	66.7	-
Vrd	14.3	28.6	66.7	-
Ischemic alterations	3.6	-	33.3	-
Arrhythmias	14.3	-	66.7	-

N: Number of articles evaluated (case series, clinical trials and control groups of experimental interventions); MA: meglumine antimoniate; SSG: sodium stibogluconate; SSG BP88: sodium stibogluconate, Chinese fabrication (Shandong Xinhua Pharmaceutical Co.); PI: pentamidine isethionate; Vrd: ventricular repolarization disturbance; AST: aspartate aminotransferase; ALT: alanine aminotransferase.

[a] Only one case series used pentamidine mesylate.

Table 4: Frequency of clinical, laboratory and electrocardiographic adverse effects among patients treated with pentavalent antimonials and pentamidine isethionate.

Pentavalent antimonials			**Pentamidine**	
Signs and symptoms	**10-20 mg/kg/day**		**2-4 mg/kg/day**	
	N	**%**	**N**	**%**
Myalgia/arthralgia	848	48.6	289	24.9
Gastrointestinal disturbances	361	17.4	312	21.5
Headache	632	23.6	224	15.2
Anorexia	257	19.4	15	46.7
Asthenia/fatigue	127	18.9	128	21.1
Fever	430	16.7	103	8.7
Cutaneous reactions	238	5.9	38	5.3
Cardiovascular alterations	254	6.7	77	7.8
Respiratory alterations	76	10.5	40	5.0
Local pain	42	64.3	526	31.6
Itching	23	8.7	-	-
Taste alterations	154	25.3	40	17.5
Neurological alterations	103	2.9	281	4.6
Balance disturbances	77	5.2	88	22.7
Behavioral alterations	-	-	38	5.3
↑AST/ALT	268	43.3	-	-
↑Lipase/amylase	157	59.9	-	-
Leukopenia	52	7.7	-	-
Thrombocytopenia	42	7.1	-	-
Hypoglycemia	-	-	83	2.4
QTc prolongation	162	16.0	-	-
Vrd	124	25.0	-	-
Arrhythmia	61	3.3	-	-

N: Number of patients evaluated; Vrd: ventricular repolarization disturbance; AST: aspartate aminotransferase; ALT: alanine aminotransferase.

Amphotericin B

Liposomal amphotericin B was evaluated in only one case series.[64] In that study, seven patients were treated with a total dose of 18 mg/kg and mild dyspnea and erythema were observed in two patients.

Miltefosine

Oral treatment with miltefosine was used in two clinical trials. One of these studies evaluated the efficacy and safety of the drug administered at a daily dose of 50 mg for 28 days for the treatment of cutaneous leishmaniasis caused by *L. (L.) mexicana* and *L. (V.) braziliensis*. The intervention included 49 patients from Colombia and 40 from Guatemala.[65] The clinical adverse effects reported were vomiting (63%), nausea (36%), kinetosis (29%), headache (27%), and diarrhea (11%). One patient presented severe headache and kinetosis and discontinued the medication on the penultimate day of treatment. A mild to moderate increase in aminotransferases and creatinine was observed in 10% and 31% of patients, respectively. In another clinical trial conducted in Colombia on 72 patients, Soto *et al*[66] compared four different doses of miltefosine. The main adverse effects (kinetosis, vomiting and elevated aminotransferases) were more frequent and intense in the groups receiving the higher dose (150 mg/day). One patient receiving high doses reported mild to moderate abdominal pain.

Discussion

This systematic review provides information regarding the safety of treatment of 4,359 patients of different ages with cutaneous leishmaniasis caused by eight different *Leishmania*

species in 12 countries of the New World. One case series should be highlighted in which *L. (L.) chagasi*, the causative agent of visceral leishmaniasis, was identified as the cause of one case of cutaneous leishmaniasis.[24]

Although randomized clinical trials are considered to be the gold standard for the evaluation of the efficacy of interventions, case series and case reports were also included since rare and severe adverse effects are frequently reported in these studies. In addition, clinical trials tend to exclude older adults, patients with chronic diseases and other individuals who present a higher risk for adverse effects.[15]

Despite the broad and meticulous search of 10 databases using carefully selected keywords, with coverage of the grey literature and no language restriction, only 65 articles containing data about adverse effects were approved.

Therapeutic trials in humans should follow the guidelines of good clinical practice and adequately report adverse effects.[83,84] However, inadequate monitoring of clinical, laboratory and electrocardiographic adverse effects, as well as the lack of classification according to criteria of severity, was a constant finding in the articles evaluated. As a consequence, instead of reporting adverse effects individually, it was necessary to categorize them into gastrointestinal disturbances, cardiovascular alterations, neurological alterations, taste alterations, and cutaneous reactions, among others.

As shown in Table 1, the frequencies of one or more adverse effects were reported in 44 articles (indicated by an asterisk in Table 1). However, divergences among frequencies were expressive. The most common adverse effects were arthralgias and myalgias, which were reported consistently. Other effects such as itching, respiratory alterations and balance disturbances were reported less regularly. Some studies limited their safety results to vague statements such as “no adverse effect was observed” or “the drugs were well tolerated”. Thus, the true frequency of the adverse effects shown in Table 4 might be underestimated. In the

remaining articles, adverse effects were cited without reporting their respective frequencies. We chose to complete the information with Tables 2 and 3, which show the number of articles reporting adverse effects according to the drug used for the treatment of cutaneus leishmaniasis in the New World.

Despite the small number of drugs used in the studies included in this review (meglumine antimoniate, sodium stibogluconate from different manufacturers, pentamidine isethionate and mesylate, liposomal amphotericin B, and miltefosine), we observed a wide variability in the therapeutic regimens employed. As a consequence, the adverse effects of pentavalent antimonials and pentamidine needed to be considered jointly, irrespective of formulation, daily dose, duration of treatment and route of administration.

Mild to moderate clinical, laboratory and electrocardiographic adverse effects were frequent. In some cases, these effects were severe, resulting in temporary or definitive treatment discontinuation, or even in death.[48-50] The profile of adverse effects of pentavalent antimonials, pentamidine and miltefosine was established and their frequencies were estimated, whenever possible.

Pentavalent antimonials were used for the treatment of 66.5% (n = 2,900) of the patients. Of these, 78.4% (n = 2,273) received standard doses of 10 to 20 mg Sb^{5+}/kg/day. High frequencies of mild to moderate adverse effects were observed. Hepatic and pancreatic abnormalities were transient and returned to normal after the end of treatment. QTc interval prolongation, a condition that, if not detected early, may cause sudden and fatal arrhythmia, was the most frequent electrocardiographic adverse effect.

Pentamidine was used in 29.6% (n = 1,291) of the patients. Of these, 63% (n = 813) received doses of 2 to 4 mg/day. Treatment with pentamidine has also been associated with a high incidence of adverse effects. Although hypoglycemia and insulin-dependent diabetes are expected adverse effects, hypoglycemia was observed in only two of 93 cases, one of them

severe.[5,57,63] No case of diabetes was reported. Total pentamidine doses higher than 1 g are believed to cause diabetes mellitus.[5] However, the total dose administered could not be established in the patients studied. A high frequency of rhabdomyolysis was reported in one of the studies; however, the authors only used elevated creatine phosphokinase 2 and 15 days after treatment as a diagnostic criterion.[60] The absence of observation of laboratory adverse effects such as elevated liver and pancreatic enzymes, as well as of electrocardiographic adverse effects (Table 4), might be due to the lack of these exams or inadequate routine monitoring of adverse effects. Electrocardiographic evaluation was performed in only one study.[58]

In Brazil, amphotericin B deoxycholate is the first-choice drug for the treatment of pregnant women and the second choice when no response to treatment with pentavalent antimonials is obtained or when their use is not possible.[5] Classically, amphotericin B has been associated with a high frequency of moderate to severe adverse effects.[85] The few studies identified in this review on the use of this drug for the treatment of American tegumentary leishmaniasis analyzed patients with the cutaneous and mucosal form together. These studies were excluded from the present review, which was restricted to the cutaneous form. The only publication included described mild adverse effects in two of seven patients treated with liposomal amphotericin B.[64] It was therefore not possible to evaluate the safety profile of different amphotericin B formulations. Although liposomal amphotericin B has not yet been approved for the treatment of cutaneous leishmaniasis in some countries such as Brazil, the drug might be indicated in cases in which other therapeutic options (pentavalent antimonials, amphotericin B deoxycholate and pentamidine) have failed or are contraindicated.[5]

Miltefosine is a promising drug recently introduced for the treatment of visceral leishmaniasis in the Old World. The use of this drug for the treatment of American

tegumentary leishmaniasis is being investigated. The main adverse effects of the drug are related to its oral administration, affecting the gastrointestinal tract, in addition to the observation of elevated aminotransferase and creatine phosphokinase levels.[65,66,86] In contrast to the studies using pentavalent antimonials, amphotericin and pentamidine, trials employing miltefosine have followed the guidelines of good clinical practice. This fact has permitted the short-term accumulation of evidence regarding the safety of this drug.

The drugs used for the treatment of cutaneous leishmaniasis are administered parenterally and are associated with a high frequency of adverse effects. The heterogeneity of studies and multiple safety outcomes reported in an incomplete and non-standardized manner did not permit to obtain combined measures for a meta-analysis in this review.

This review highlights the need for the application of defined criteria to the data collection on adverse effects in observational studies, as well as the need for clinical trials employing drugs already used for the treatment of American tegumentary leishmaniasis. Such studies should evaluate adverse effect using well-defined criteria for the classification of severity. We recommend the monitoring of clinical, laboratory and electrocardiographic adverse effects at a minimum interval of 10 days during treatment and on day 30 after the end of treatment, irrespective of the therapeutic regimen adopted. Monitoring should include a complete blood count and the measurement of urea, creatinine, glucose, electrolytes and liver and pancreatic enzymes, in addition to an electrocardiogram.

Contributors

LFGO and MFMM developed the searches strategy. Selection of articles and date extraction were performed by LFGO, AOS and CAFA. The paper was written by LFGO, AOS and CAFA with input from MFMM, SRLP, RVCO and MCAM.

Conflicts of interest

We declare that we have no conflicts of interest.

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References

1. Marzochi MAC, Marzochi KBF. Tegumentary and visceral leishmaniasis in Brazil: emerging anthropozoonosis and possibilities for their control. *Cad Saude Publica*. 1994;10 Suppl 2:S359-S375.

2. WHO. Report of the Consultative Meeting on Cutaneous Leishmaniasis. Geneva: WHO; 2007.

3. Jones TC, Johnson WD Jr, Barretto AC, Lago E, Badaro R, Cerf B, Reed SG, Netto EM, Tada MS, Franca TF, et al. Epidemiology of American cutaneous leishmaniasis due to Leishmania braziliensis braziliensis. *J Infect Dis.* 1987 Jul;156(1):73-83.

4. Lainson R. The American leishmaniases: some observations on their ecology and epidemiology. *Trans R Soc Trop Med Hyg.* 1983;77(5):569-96.

5. Brasil. Ministério da Saúde. Manual de Vigilância da Leishmaniose Tegumentar Americana. 3rd ed. Brasília (DF);2010.

6. Herwaldt BL. Leishmaniasis. *Lancet* 1999 Oct 2;354(9185):1191-9.

7. Herwaldt BL, Berman JD. Recommendation for treating leishmaniasis with sodium stibogluconate (Pentostam) and review of pertinent clinical studies. *Am J Trop Med Hyg.* 1992 Mar;46(3):296-306.

8. Berman JD**.** Chemotherapy *for* leishmaniasis: biochemical mechanisms, clinical efficacy, and future strategies. *Rev Infect Dis*. 1988 May-Jun;10(3):560-86.

9. Gonzáles U, Pinart M, Reginfo-Pardo M, Macaya A, Alvar J, Tweed JA. Interventions for American cutaneous and mucocutaneous leishmaniasis. *Cochrane Database Syst Rev*. 2009 Apr 15;(2):CD004834.

10. Tuon FF, Amato VS, Graf MS, Siqueira AM, Nicodemo AC, Amato Neto V. Treatment of New World cutaneous leishmaniasis – a systematic review with a meta-analysis. *Int J Dermatol*. 2008 Feb;47(2):109-124.

11. Lima EB, Porto C, Motta JOC, Sampaio RNR. Tratamento da leishmaniose tegumentar americana. *An bras dermatol*. 2007; 82(2):111-24.

12. Romero GAS, Hueb M, D'Oliveira Jr A, Schubach A. Simpósio sobre Tratamento das Leishmanioses. *Rev Soc Bras Med Trop*. 2001;34:58-68.

13. Deeks JJ, Higgins, JPT, Altman DG, editors. Including Adverse effects. In: Higgins JPT, Green S, editors. Cochrane Handbook for Systematic Reviews of Interventions 4.2.6 [updated September 2006]; Appendix 6b. The Cochrane Library, Issue 4, 2006. Chichester, UK: John Wiley & Sons, Ltd.

14. Kane-Gill S, Rea RS, Verrico MM, Weber RJ. Adverse-drug- event rates for high-cost and high-use drugs in the intensive care unit. Am J Health Syst Pharm. 2006 Oct 1;63(19):1876-81.

15. Loke Y K, Price D, Herxheimer A. Systematic reviews of adverse effects: framework for a structural approach. *BMC Med Res Methodol*. 2007;7:32. http://www.biomedcenter.com/1471-2288/7/32 (accessed April 23, 2008).

16. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JP, Clarke M, Devereaux PJ, Kleijnen J, Moher D. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *Ann Intern Med*. 2009 Aug 18;151(4):W65-94.

17. Division of AIDS table for grading the severity of adults and pediatric adverse events publish date: December, 2004. http://www.ucdmc.ucdavis.edu?clinicaltrials/documents/DAIDS_AE_gradingTable_FinalDec2004.pdf (accessed May 25, 2009)

18. Oliveira-Neto MP, Schubach AO, Mattos M, Gonçalves-Costa SC, Pirmez C. A low-dose antimony treatment in 159 patients with American cutaneous leishmaniasis: extensive follow-up studies (up to 10 years). *Am J Trop Med Hyg*. 1997 Dec;57(6):651-5.

19. Oliveira-Neto MP, Schubach AO, Mattos M, Gonçalves-Costa SC, Pirmez C. Treatment of American cutaneous leishmaniasis: a comparison between low dosage (5 mg/kg/day) and high dosage (20 mg/kg/day) antimony regimens. *Pathol Biol (Paris)*. 1997 Jun;45(6):496-9.

20. Kopke LFF, Vale ECS, Araújo MG, Magalhães PA, Furtado T. Tratamento da leishmaniose tegumentar americana pelo antimoniato de N-metil-glucamina: estudo duplo-cego com doses de 14mg/Kg/dia e 28mg/Kg/dia de antimoniato. *An bras dermatol.* 1991;66(2):87-94.

21. Oliveira-Neto MP, Mattos Mda S. An alternative antimonial schedule to be used in cutaneous leishmaniasis when high doses of antimony are undesirable. *Rev Soc Bras Med Trop*. 2006 Jul-Aug;39(4):323-6.

22. Hepburn NC, Tidman MJ, Hunter JA. Cutaneous leishmaniasis in British troops from Belize. *Br J Dermatol.* 1993 Jan;128(1):63-8.

23. Navin TR, Arana BA, Arana FE, Mérida AM, Castillo AL, Pozuelos JL. Placebo-controlled clinical trial of meglumine antimonate (glucantime) vs. localized controlled heat in the treatment of cutaneous leishmaniasis in Guatemala. *Am J Trop Med Hyg.* 1990 Jan;42(1):43-50.

24. Chulay JD, Oster CN, McGreevy PB, Hendricks LD, Kreutzer RD. American cutaneous leishmaniasis: presentation and problems of patient management. *Rev Soc Bras Med Trop*. 1988 Oct-Dec;21(4):165-72.

25. Oster CN, Chulay JD, Hendricks LD, Pamplin CL 3rd, Ballou WR, Berman JD, Takafuji ET, Tramont EC, Canfield CJ. American cutaneous leishmaniasis: a comparison of three sodium stibogluconate treatment schedules. *Am J Trop Med Hyg*. 1985 Sep;34(5):856-60.

26. Henderson A, Jolliffe D. Cardiac effects of sodium stibogluconate. *Br J Clin Pharmacol*. 1985 Jan;19(1):73-7.

27. Passos VMA, Barreto SM, Romanha AJ, Krettli AU, Volpini AC, Gontijo CMF et al. Leishmaniose tegumentar na região metropolitana de Belo Horizonte: aspectos clínicos, laboratoriais, terapêuticos e evolutivos (1989-1995). *Rev Soc Bras Med Trop*. 2001;34(1):5-12.

28. Seaton RA, Morrison J, Man I, Watson J, Nathwani D. Out-patient parenteral antimicrobial therapy--a viable option for the management of cutaneous leishmaniasis. *QJM*. 1999 Nov;92(11):659-67.

29. Wortmann GW, Aronson NE, Byrd JC, Grever MR, Oster CN. Herpes zoster and lymphopenia associated with sodium stibogluconate therapy for cutaneous leishmaniasis. *Clin Infect Dis.* 1998 Sep;27(3):509-12.

30. Krolewiecki AJ, Romero HD, Cajal SP, Abraham D, Mimori T, Matsumoto T, Juarez M, Taranto NJ. A randomized clinical trial comparing oral azithromycin and meglumine antimoniate for the treatment of American cutaneous leishmaniasis caused by Leishmania (Viannia) braziliensis. *Am J Trop Med Hyg*. 2007 Oct;77(4):640-6.

31. Arana BA, Navin TR, Arana FE, Berman JD, Rosenkaimer F. Efficacy of a short course (10 days) of high-dose meglumine antimonate with or without interferon-gamma in treating cutaneous leishmaniasis in Guatemala. *Clin Infect Dis*. 1994 Mar;18(3):381-4.

32. Navin TR, Arana BA, Arana FE, Berman JD, Chajón JF. Placebo-controlled clinical trial of sodium stibogluconate (Pentostam) versus ketoconazole for treating cutaneous leishmaniasis in Guatemala. *J Infect Dis.* 1992 Mar;165(3):528-34.

33. Wortmann G, Miller RS, Oster C, Jackson J, Aronson N. A randomized, double-blind study of the efficacy of a 10- or 20-day course of sodium stibogluconate for treatment of cutaneous leishmaniasis in United States military personnel. *Clin Infect Dis*. 2002 Aug 1;35(3):261-7.

34. Saldanha ACR, Romero GAS, Guerra C, Merchan-Hamann E, Macedo VO. Estudo comparativo entre estibogluconato de sódio BP 88® e antimoniato de meglumina no tratamento da leishmaniose cutânea: toxidade bioquímica e cardíaca. *Rev Soc Bras Med Trop*. 2000;33(4):383-8.

35. Martinez S, Gonzalez M, Vernaza ME. Treatment of cutaneous leishmaniasis with allopurinol and stibogluconate. *Clin Infect Dis*. 1997 Feb;24(2):165-9.

36. Soto J, Valda-Rodriquez L, Toledo J, Vera-Navarro L, Luz M, Monasterios-Torrico H, Vega J, Berman J. Comparison of generic to branded pentavalent antimony for treatment of new world cutaneous leishmaniasis. *Am J Trop Med Hyg*. 2004 Nov;71(5):577-81.

37. Scope A, Trau H, Anders G, Barzilai A, Confino Y, Schwartz E. Experience with New World cutaneous leishmaniasis in travelers. *J Am Acad Dermatol*. 2003 Oct;49(4):672-8.

38. Deps PD, Viana MC, Falqueto A, Dietze R. Avaliação comparativa da eficácia e toxicidade do antimoniato de N-metil-glucamina e do estibogluconato de Sódio BP88© no tratamento da leishmaniose cutânea localizada. *Rev Soc Bras Med Trop*. 2000;33(6):535-543.

39. Zlotogorski A, Gilead L, Jonas F, Horev L, Klaus SN. South American cutaneous leishmaniasis: report of ten cases in Israeli travelers. *J Eur Acad Dermatol Venereol*. 1998 Jul;11(1):32-6.

40. Gasser RA Jr, Magill AJ, Oster CN, Franke ED, Grögl M, Berman JD. Pancreatitis induced by pentavalent antimonial agents during treatment of leishmaniasis. *Clin Infect Dis*. 1994 Jan;18(1):83-90.

41. Name RQ, Sampaio JHD, Borges KT, Tauil PL, Nogueira LSC, Sampaio RNR. Estudo clínico, epidemiologico e terapêutico de 402 pacientes com leishmaniose tegumentar americana atendidos no Hospital Universitário de Brasilia, DF, Brasil. *An bras dermatol.* 2005;80(3):249-254.

42. De Paula CDR, Sampaio JHD, Cardoso DR, Sampaio RNR. Estudo comparativo da eficácia de isotionato de pentamidina administrada em três doses durante uma semana e de N-metil-glucamina 20mgSbV/kg/dia durante 20 dias para o tratamento da forma cutânea da leishmaniose tegumentar americana. *Rev Soc Bras Med Trop*. 2003;36(3):365-371.

43. Hepburn NC, Tidman MJ, Hunter JA. Aminosidine (paromomycin) versus sodium stibogluconate for the treatment of American cutaneous leishmaniasis. *Trans R Soc Trop Med Hyg.* 1994 Nov-Dec;88(6):700-3.

44. Saldanha ACR, Romero GAS, Merchan-Hamann E, Magalhães AV, Macedo VO. Estudo comparativo entre estibogluconato de sódio BP88® e antimoniato de meglumina no tratamento da leishmaniose cutânea: eficácia e segurança. *Rev Soc Bras Med Trop*. 1999;32(4):383-7.

45. Convit J, Castellanos PL, Rondon A, Pinardi ME, Ulrich M, Castes M, Bloom B, Garcia L. Immunotherapy versus chemotherapy in localised cutaneous leishmaniasis. *Lancet*. 1987 Feb 21;1(8530):401-5.

46. Hepburn NC. Thrombocytopenia complicating sodium stibogluconate therapy for cutaneous leishmaniasis. *Trans R Soc Trop Med Hyg*. 1993 Nov-Dec;87(6):691.

47. Oliveira-Neto MP, Mattos M, Cuzzi-Maya T, Pirmez C. Paniculite eosinofílica localizada em conseqüência de injeções intramusculares de composto de antimônio pentavalente para o tratamento de leishmaniasis tegumentar americana. *An bras Dermatol*. 2004;79(4):463-9.

48. Kopke LFF, Café MEM, Neves LB, Scherrer MAR, Machado-Pinto J, Souza MSLA, et al. Morte após uso de antimonial pentavalente em leishmaniose tegumentar americana. *An bras dermatol.* 1993;68(5):259-261.

49. Rodrigues ML, Costa RS, Souza CS, Foss NT, Roselino AM. Nephrotoxicity attributed to meglumine antimoniate (Glucantime) in the treatment of generalized cutaneous leishmaniasis. *Rev Inst Med Trop Sao Paulo*. 1999 Jan-Feb;41(1):33-7.

50. Costa JML, Garcia AM, Rêbelo JMM, Guimarães KM, Guimarães RM, Nunes PMS. Óbito durante tratamento da leishmaniose tegumentar americana com stibogluconato de sódio bp 88® (shandong xinhua). *Rev Soc Bras Med Trop*. 2003;36(2):295-8.

51. Oliveira-Neto MP, Schubach A, Mattos M, da Costa SC, Pirmez C. Intralesional therapy of American cutaneous leishmaniasis with pentavalent antimony in Rio de Janeiro, Brazil--an area of Leishmania (V.) braziliensis transmission. *Int J Dermatol*. 1997 Jun;36(6):463-8.

52. Gadelha AR, Oliveira WC, Assunção IJ, Dourado HV. Tratamento da leishmaniose tegumentar americana com injeções intralesionais de N-metil-glucamina. *An Bras Dermatol*. 1990;65(4):201-3.

53. Barrios LA, Costa JM, Netto EM, Vexenat CO, Cuba CC, Marsden PD. Intralesional glucantime in Leishmania braziliensis braziliensis infections. *Trans R Soc Trop Med Hyg*. 1986;80(1):173-4.

54. Roussel M, Nacher M, Frémont G, Rotureau B, Clyti E, Sainte-Marie D, Carme B, Pradinaud R, Couppié P. Comparison between one and two injections of pentamidine isethionate, at 7 mg/kg in each injection, in the treatment of cutaneous leishmaniasis in French Guiana. *Ann Trop Med Parasitol*. 2006 Jun;100(4):307-14.

55. Robledo SM, Puerta JA, Muñoz DL, Guardo M, Velez ID. Eficacia y tolerancia de la pentamidina en el tratamiento de la leishmaniasis cutánea producida por Leishmania (V.) panamensis en Colombia. *Biomedica* 2006;26 Suppl 1:188-193.

56. Nacher M, Carme B, Sainte Marie D, Couppié P, Clyti E, Guibert P, Pradinaud R. Influence of clinical presentation on the efficacy of a short course of pentamidine in the treatment of cutaneous leishmaniasis in French Guiana. *Ann Trop Med Parasitol*. 2001 Jun;95(4):331-6.

57. Soto J, Buffet P, Grogl M, Berman J. Successful treatment of Colombian cutaneous leishmaniasis with four injections of pentamidine. *Am J Trop Med Hyg*. 1994 Jan;50(1):107-11.

58. Dimier-David L, Valda L, Inofuentes A, Mallea F, David C, Dedet JP. Traitement de la lésion cutanée de la leishmaniose à Leishmania braziliensis: échec de l'isethionate de pentamidine. *Med Mal Infect.* 1992;22(12):1183-1186.

59. Talhari S, Sardinha JCG, Schettini APM, Arias J, Naiff RD. Tratamento da leishmaniose tegumentar americana: resultados preliminares com a pentamidina. *An bras dermatol.* 1985;60(6):361-4.

60. Delobel P, Pradinaud R. Rhabdomyolysis associated with pentamidine isethionate therapy for American cutaneous leishmaniasis. *J Antimicrob Chemother*. 2003 May;51(5):1319-20.

61. Andersen EM, Cruz-Saldarriaga M, Llanos-Cuentas A, Luz-Cjuno M, Echevarria J, Miranda-Verastegui C, Colina O, Berman JD. Comparison of meglumine antimoniate and pentamidine for peruvian cutaneous leishmaniasis. *Am J Trop Med Hyg*. 2005 Feb;72(2):133-7.

62. Lai A Fat EJ, Vrede MA, Soetosenojo RM, Lai A Fat RF. Pentamidine, the drug of choice for the treatment of cutaneous leishmaniasis in Surinam. *Int J Dermatol*. 2002 Nov;41(11):796-800.

63. Soto-Mancipe J, Grogl M, Berman JD. Evaluation of pentamidine for the treatment of cutaneous leishmaniasis in Colombia. *Clin Infect Dis.* 1993 Mar;16(3):417-25.

64. Solomon M, Baum S, Barzilai A, Scope A, Trau H, Schwartz E. Liposomal amphotericin B in comparison to sodium stibogluconate for cutaneous infection due to Leishmania braziliensis. *J Am Acad Dermatol*. 2007 Apr;56(4):612-6.

65. Soto J, Arana BA, Toledo J, Rizzo N, Vega JC, Diaz A, Luz M, Gutierrez P, Arboleda M, Berman JD, Junge K, Engel J, Sindermann H. Miltefosine for new world cutaneous leishmaniasis. *Clin Infect Dis.* 2004 May 1;38(9):1266-72.

66. Soto J, Toledo J, Gutierrez P, Nicholls RS, Padilla J, Engel J, Fischer C, Voss A, Berman J. Treatment of American cutaneous leishmaniasis with miltefosine, an oral agent. *Clin Infect Dis*. 2001 Oct 1;33(7):E57-61.

67. Correia D, Macêdo O, Carvalho EM, Barral A, Magalhães AV, Abreu MVA, et al. Estudo comparativo entre antimoniato de meglumina, isotianato de pentamidina e sulfato de aminosidina, no tratamento de lesões cutâneas primárias causadas por Leishmania (Viannia) braziliensis. *Rev Soc Bras Med Trop.* 1996;29(5):447-53.

68. Ballou WR, McClain JB, Gordon DM, Shanks GD, Andujar J, Berman JD, Chulay JD. Safety and efficacy of high-dose sodium stibogluconate therapy of American cutaneous leishmaniasis. *Lancet.* 1987 Jul 4;2(8549):13-6.

69. Palacios R, Osorio LE, Grajalew LF, Ochoa MT. Treatment failure in children in a randomized clinical trial with 10 and 20 days of meglumine antimonate for cutaneous leishmaniasis due to Leishmania viannia species. *Am J Trop Med Hyg.* 2001 Mar-Apr;64(3-4):187-93.

70. Sáenz RE, Paz HM, Johnson CM, Narvaez E, Vásquez AM. Evaluacion de la efectividad y toxicidad del pentostam y del glucantime em el tratamiento de la leishmaniasis cutânea. *Rev Méd Panamá* 1987;12:148-57.

71. Arevalo I, Tulliano G, Quispe A, Spaeth G, Matlashewski G, Llanos-Cuentas A, Pollack H. Role of imiquimod and parenteral meglumine antimoniate in the initial treatment of cutaneous leishmaniasis. *Clin Infect Dis*. 2007 Jun 15;44(12):1549.

72. Armijos RX, Weigel MM, Calvopiña M, Mancheno M, Rodriguez R. Comparison of the effectiveness of two topical paromomycin treatments versus meglumine antimoniate for New World cutaneous leishmaniasis. *Acta Trop*. 2004 Jul;91(2):153-60.

73. Velez I, Agudelo S, Hendrickx E, Puerta J, Grogl M, Modabber F, Berman J. Inefficacy of allopurinol as monotherapy for Colombian cutaneous leishmaniasis. A randomized, controlled trial. *Ann Intern Med.* 1997 Feb 1;126(3):232-6.

74. Hepburn NC, Siddique I, Howie AF, Beckett GJ, Hayes PC. Hepatotoxicity of sodium stibogluconate therapy for American cutaneous leishmaniasis. *Trans R Soc Trop Med Hyg.* 1994 Jul-Aug;88(4):453-5.

75. Martinez S, Marr JJ. Allopurinol in the treatment of American cutaneous leishmaniasis. *N Engl J Med.* 1992 Mar 12;326(11):741-4.

76. Saenz RE, Paz H, Berman JD. Efficacy of ketoconazole against Leishmania braziliensis panamensis cutaneous leishmaniasis. *Am J Med*. 1990 Aug;89(2):147-55.

77. Romero GA, Flores M RM, Noronha EF, Macêdo Vde O. High frequency of skin reactions in patients with leishmaniasis treated with meglumine antimoniate contaminated with heavy metals: a comparative approach using historical controls. *Mem Inst Oswaldo Cruz*. 2003 Jan;98(1):145-9.

78. Romero GAS, Guerra MVF, Paes MG, Macêdo VO. Comparison of Cutaneous Leishmaniasis due to Leishmania (Viannia) braziliensis and L. (V) guyanensis in Brazil: Therapeutics response to Meglumine Antimoniate. *Am J Trop Med Hyg*. 2001;65(5):456-65.

79. Ribeiro AL, Drummond JB, Volpini AC, Andrade AC, Passos VM. Electrocardiographic changes during low-dose, short-term therapy of cutaneous leishmaniasis with the pentavalent antimonial meglumine. *Braz J Med Biol Res*. 1999 Mar;32(3):297-301.

80. Lawn SD, Armstrong M, Chilton D, Whitty CJ. Electrocardiographic and biochemical adverse effects of sodium stibogluconate during treatment of cutaneous and mucosal leishmaniasis among returned travellers. *Trans R Soc Trop Med Hyg*. 2006 Mar;100(3):264-9.

81. Hepburn NC, Nolan J, Fenn L, Herd RM, Neilson JM, Sutherland GR, Fox KA. Cardiac effects of sodium stibogluconate: myocardial, electrophysiological and biochemical studies. *QJM*. 1994 Aug;87(8):465-72.

82. Koerber WA, Koehn MC, Jacobs PH, Russell BJ. Treatment of Cutaneous Leishmaniasis With Antimony Sodium Gluconate. *Arch Dermatol*. 1978 Aug; 114:1226.

83. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human use. Clinical Safety Data Management: Definitions and Standards for Expedited Reporting E2A (ICH E2A). [cited 1994 Oct 27]. http://www.ich.org/cache/ compo/276-254-1.html.

84. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human use. ICH Harmonised Tripartite Guideline. Guideline for Good Clinical Practice (GCP) E6(R1) Version 10. [cited June 1996]. http://www.ich.org/LOB/media/MEDIA482.pdf

85. Bennett JE. Antimicrobial: antifungal agents. In: Goodman, LS, Gilman A, Brunton LL, Lazo JS, Parker KL, eds. Goodman and Gilman's the pharmacological basis of therapeutics. 11th ed. New York: The McGraw-Hill Companies; 2006. Chap. 48, Page 1225-1242.

86. Berman JJ. Treatment of leishmaniasis with miltefosine: 2008 status. *Expert Opin Drug Metab Toxicol*. 2008 Sep;4(9):1209-16.

APPENDIX 1

Search strategy

Pubmed: *((("antimony/adverse effects"[MeSH Terms] OR "antimony sodium gluconate/adverse effects"[MeSH Terms]) OR "antiprotozoal agents/adverse effects"[MeSH Terms] OR "meglumine/adverse effects"[MeSH Terms] OR "paromomycin/adverse effects"[MeSH Terms] OR "pentamidine/adverse effects"[MeSH Terms] OR "azithromycin/adverse effects"[MeSH Terms] OR "itraconazole/adverse effects"[MeSH Terms] OR "organometallic compounds/adverse effects"[MeSH Terms] OR "allopurinol/adverse effects"[MeSH Terms] OR "ketoconazole/adverse effects"[MeSH Terms] OR "trypanocidal agents/adverse effects"[MeSH Terms] OR "mefloquine/adverse effects"[MeSH Terms]) OR (PENTAMIDINE ISETHIONATE AND "adverse effects"[MeSH Subheading])) AND ("leishmaniasis, cutaneous/drug therapy"[MeSH Terms] NOT "leishmaniasis, mucocutaneous"[MeSH Terms]) AND "leishmaniasis, cutaneous/drug therapy"[MeSH Major Topic] AND ((Humans[Mesh]));*

Embase: [**#1 AND #2 AND #3] #1** *'antimony'/exp OR 'antimony sodium gluconate'/exp OR antiprotozoal OR 'meglumine'/exp OR 'paromomycin'/exp OR 'pentamidine'/exp OR 'azithromycin'/exp OR 'itraconazole'/exp OR 'organometallic compounds'/exp OR 'allopurinol'/exp OR 'ketoconazole'/exp OR trypanocidal OR 'mefloquine'/exp OR 'pentamidine isethionate'/exp AND [2002-2009]/py* **#2***'leishmaniasis cutaneous' OR 'cutaneous leishmaniasis'/exp AND [2002-2009]/py1,773***#3** *'adverse effects' OR 'side effects' OR 'adverse drug reaction'/exp AND [2002-2009]/py*;

Scopus: *(TITLE-ABS-KEY(antimony OR "antimony sodium gluconate" OR antiprotozoal OR meglumine OR paromomycin OR pentamidine OR azithromycin OR itraconazole OR "organometallic compounds" OR allopurinol OR ketoconazole OR trypanocidal OR mefloquine OR "PENTAMIDINE ISETHIONATE") AND TITLE-ABS-KEY((leishmaniasis AND cutaneous) AND ("Adverse effects" OR "side effects" OR "adverse drug reaction")))*;

Web of Science *(antimony OR "antimony sodium gluconate" OR antiprotozoal OR meglumine OR paromomycin OR pentamidine OR azithromycin OR itraconazole OR*

"organometallic compounds" OR allopurinol OR ketoconazole OR trypanocidal OR mefloquine OR "PENTAMIDINE ISETHIONATE") AND Topic=((leishmaniasis AND cutaneous) AND ("Adverse effects" OR "side effects" OR "adverse drug reaction")) Timespan=All Years;

Science direct *pub-date > 1822 and TITLE-ABSTR-KEY(antimony OR "antimony sodium gluconate" OR antiprotozoal OR meglumine OR paromomycin OR pentamidine OR azithromycin OR itraconazole OR "organometallic compounds" OR allopurinol OR ketoconazole OR trypanocidal OR mefloquine OR "PENTAMIDINE ISETHIONATE") and TITLE-ABSTR-KEY((leishmaniasis AND cutaneous) AND ("Adverse effects" OR "side effects" OR "adverse drug reaction"))*;

LILACS *"LEISHManiose cutanea" or "LEISHManiose do novo mundo" [Descritor de assunto] and antimon$ OR antiprotoz$ OR meglumin$ OR paromom$ OR pentamidin$ OR azitromi$ R itraconazol$ OR organometal$ OR alopurinol OR Cetoconazol$ OR tripanocid$ OR mefloquin$ [Palavras] and (advers$ or reacao or reaction) and humano$ [Palavras]*;

Scielo *(antimony OR "antimony sodium gluconate" OR antiprotozoal OR meglumine OR paromomycin OR pentamidine OR azithromycin OR itraconazole OR "organometallic compounds" OR allopurinol OR ketoconazole OR trypanocidal OR mefloquine OR "PENTAMIDINE ISETHIONATE") and leishm$ AND cutan$ AND Advers$*;

Cochrane *(Leishmaniasis and cutaneous and treatment)*.

Scirus (*Leishmaniasis and cutaneous and treatment and adverse effects or adverse drug reaction or side effects)*

Highwirepress *(adverse effects and antimony sodium gluconate and antiprozoal agents and leishmaniasis)*

APPENDIX 2

CODE: _____

DATA EXTRACTION FORM FOR THE ARTICLE CL IN THE NEW WORLD

REVIEWERS:

1. AOS/LFGO ( ) 2. CAFA/LFGO ( )
3. LFGO/AOS/CAFA ( )

COMMENT:

1. Approved ( ) 2. Excluded ( )

Reason (2):_____
_____

1. DATA OF THE PUBLICATION

TITLE:_____
_____

AUTHORS:_____

COMPLETE REFERENCE:_____
_____

ROUTE OF RETRIEVAL:

1. Electronic search ( ) 2. Cross-reference ( ) 3. Contact with the authors ( )

2. TYPE OF STUDY

1. Case report ( ) 2. Case series ( ) 3. Case control study 4. Clinical trial ( )
5. Cohort ( ) 6. Other ( ) _____

No. Interventions: _____

3. DESCRIPTION OF INTERVENTION 1

DRUG:

1. Glucantime ( ) 2. Pentostam ( ) 3. Sodium stibogluconate ( ) 4. Meglumine antimoniate ( )
5. Pentamidine mesylate ( ) 6. Pentamidine isethionate ( ) 7. Amphotericin B ( )
8. Miltefosine ( ) 9. Other ( ) _____

ROUTE OF ADMINISTRATION:

1. IM ( ) 2. IV ( ) 3. VO ( )

DOSAGE:_____

DURATION OF TREATMENT:_____

TOTAL DOSE:_____ **UNIT:** _____ **No. PARTICIPANTS:**_____

3. DESCRIPTION OF INTERVENTION 2

DRUG:

1. Glucantime ( ) **2. Pentostam ( )** **3. Sodium stibogluconate ( )** **4. Meglumine antimoniate ( )**

5. Pentamidine mesylate ( ) **6. Pentamidine isethionate ( )** **7. Amphotericin B ( )**

8. Miltefosine ( ) **9. Other ( )** _____

ROUTE OF ADMINISTRATION:

1. IM ( ) **2. IV ( )** **3. VO ( )**

DOSAGE:_____

DURATION OF TREATMENT:_____

TOTAL DOSE:_____ **UNIT:** _____ **No. PARTICIPANTS:**_____

3. DESCRIPTION OF INTERVENTION 3

DRUG:

1. Glucantime ( ) **2. Pentostam ( )** **3. Sodium stibogluconate ( )** **4. Meglumine antimoniate ( )**

5. Pentamidine mesylate ( ) **6. Isethionate pentamidine ( )** **7. Amphotericin B ( )**

8. Miltefosine ( ) **9. Other ( )** _____

ROUTE OF ADMINISTRATION:

1. IM ( ) **2. IV ( )** **3. VO ( )**

DOSAGE:_____

DURATION OF TREATMENT:_____

TOTAL DOSE:_____ **UNIT:** _____ **No. PARTICIPANTS:**_____

4. PARTICIPANTS

INCLUSION CRITERIA: _____

_____

_____

EXCLUSION CRITERIA: _____

_____

_____

GEOGRAPHIC ORIGIN:

1. Brazil ( ) 2. Chile ( ) 3. Mexico ( ) 4. Guiana ( ) 5. French Guiana ( )
6. Suriname ( ) 7. Peru ( ) 8. Panama ( ) 9. Belize ( ) 10. Colombia ( )
11. Venezuela ( ) 12. Guatemala ( ) 13. Bolivia ( ) 14. Argentina ( )
Other ( ) _____

AGE RANGE (years):

1. 0 to 14 ( ) 2. 15 to 19 ( ) 3. 20 to 59 ( ) 4. 60 or older ( ) 9. No age range ( )

DISTRIBUTION ACCORDING TO GENDER: _____ **STUDY PERIOD:** From___/___/_____ to ___/___/_____

MEAN AGE: _____

5. DATA REGARDING SAFETY

CLINICAL ALTERATIONS 1

Headache ( )	Freq:__ _____	Degree: _____	Nausea ( )	Freq:__ _____	Degree: _____
Myalgias ( )	Freq:__ _____	Degree: _____	Arthralgias ( )	Freq:__ _____	Degree: _____
Local pain ( )	Freq:__ _____	Degree: _____	Fever ( )	Freq:__ _____	Degree: _____
Anorexia ( )	Freq:__ _____	Degree: _____	Dizziness ( )	Freq:__ _____	Degree: _____
Hypothermia ( )	Freq:__ _____	Degree: _____	Erythema ( )	Freq:__ _____	Degree: _____
Abdom. pain ( )	Freq:__ _____	Degree: _____	Altered taste ( )	Freq:__ _____	Degree: _____
Vomiting ( )	Freq:__ _____	Degree: _____	Diarrhea ( )	Freq:__ _____	Degree: _____
Other ( )	Freq:__ _____	Degree: _____	Which: _____		

CLINICAL ALTERATIONS 2

Headache ( )	Freq:__ _____	Degree: _____	Nausea ( )	Freq:__ _____	Degree: _____
Myalgias ( )	Freq:__ _____	Degree: _____	Arthralgias ( )	Freq:__ _____	Degree: _____
Local pain ( )	Freq:__ _____	Degree: _____	Fever ( )	Freq:__ _____	Degree: _____
Anorexia ( )	Freq:__ _____	Degree: _____	Dizziness ( )	Freq:__ _____	Degree: _____
Hypothermia ( )	Freq:__ _____	Degree: _____	Erythema ( )	Freq:__ _____	Degree: _____
Abdom. pain ( )	Freq:__ _____	Degree: _____	Altered taste ( )	Freq:__ _____	Degree: _____
Vomiting ( )	Freq:__ _____	Degree: _____	Diarrhea ( )	Freq:__ _____	Degree: _____
Other ( )	Freq:__ _____	Degree: _____	Which: _____		

CLINICAL ALTERATIONS 3

5. DATA REGARDING SAFETY 3 (Clinical alterations)

Headache ( )	Freq:__ _____	Degree: _____	Nausea ( )	Freq:__ _____	Degree: _____
Myalgias ( )	Freq:__ _____	Degree: _____	Arthralgias ( )	Freq:__ _____	Degree: _____
Local pain ( )	Freq:__ _____	Degree: _____	Fever ( )	Freq:__ _____	Degree: _____
Anorexia ( )	Freq:__ _____	Degree: _____	Dizziness ( )	Freq:__ _____	Degree: _____

Hypothermia ( )	Freq:__ _____	Degree: _____	Erythema ( )	Freq:__ _____	Degree: _____
Abdom. pain ( )	Freq:__ _____	Degree: _____	Altered taste ( )	Freq:__ _____	Degree: _____
Vomiting ( )	Freq:__ _____	Degree: _____	Diarrhea ( )	Freq:__ _____	Degree: _____
Other ( )	Freq:__ _____	Degree: _____	Which: _____		
LABORATORY ALTERATIONS 1					
Elevated ALT ( )	Freq:__ _____	Degree: _____	Elevated AST ( )	Freq:__ _____	Degree: _____
Amylase ( )	Freq:__ _____	Degree: _____	Lipase ( )	Freq:__ _____	Degree: _____
Other ( )	Freq:__ _____	Degree: _____	Which: _____		
Altered ECG ( )	Freq:__ _____	Degree: _____	Which: _____		
LABORATORY ALTERATIONS 2					
Elevated ALT ( )	Freq:__ _____	Degree: _____	Elevated AST ( )	Freq:__ _____	Degree: _____
Amylase ( )	Freq:__ _____	Degree: _____	Lipase ( )	Freq:__ _____	Degree: _____
Other ( )	Freq:__ _____	Degree: _____	Which: _____		
Altered ECG ( )	Freq:__ _____	Degree: _____	Which: _____		
LABORATORY ALTERATIONS 3					
Elevated ALT ( )	Freq:__ _____	Degree: _____	Elevated AST ( )	Freq:__ _____	Degree: _____
Amylase ( )	Freq:__ _____	Degree: _____	Lipase ( )	Freq:__ _____	Degree: _____
Other ( )	Freq:__ _____	Degree: _____	Which: _____		
Altered ECG ( )	Freq:__ _____	Degree: _____	Which: _____		

Observations:

_____
_____
_____
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_____

5. CONCLUSÕES

4.1 Os antimoniais pentavalentes foram os medicamentos mais utilizados (66,5%; n=2900) para o tratamento da leishmaniose cutânea nos estudos avaliados nesta revisão sistemática, seguidos da pentamidina (29,6%; n=1291).

4.2 As freqüências de um ou mais efeitos adversos foram relatadas em 44 estudos (67,7%), porém, houve grande discrepância entre as freqüências. Os efeitos adversos mais comuns foram artralgias e mialgias, relatados de forma consistente. Outros efeitos, como reações cutâneas e alterações respiratórias foram muito menos relatados.

4.3 Os efeitos adversos clínicos, laboratoriais e eletrocardiográficos leves a moderados foram freqüentes, ocorrendo em mais de 95% dos casos. Poucas vezes (menos de 5% dos casos), tais efeitos foram graves provocando suspensão temporária ou definitiva do tratamento, ou mesmo óbito.

4.4 Encontrou-se uma grande variabilidade de doses, vias (intravenosa, intramuscular e intralesional) e formas de administração (contínua, intermitente e dias alternados), apesar do pequeno número de medicamentos utilizados nos artigos incluídos nesta revisão (antimoniato de meglumina, estibogluconato de sódio, isotionato e mesilato de pentamidina, anfotericina B lipossomal e miltefosine).

4.5 Concluímos pela necessidade do desenvolvimento de novos medicamentos mais seguros e mais ensaios clínicos e estudos observacionais com medicamentos já utilizados para o tratamento da leishmaniose cutânea no Novo Mundo para estabelecer quais são os melhores esquemas terapêuticos. Tais estudos devem contemplar monitoração adequada dos efeitos adversos clínicos, laboratoriais e eletrocardiográficos, com critérios de classificação de gravidade.

6. REFERÊNCIAS BIBLIOGRÁFICAS

1. Marzochi MAC, Marzochi KBF. Tegumentary and visceral leishmaniasis in Brazil: emerging anthropozoonosisand possibilities for their control. *Cad Saude Publica*. 1994;10 Suppl 2:S359-S375.

2. Herwaldt BL. Leishmaniasis. *Lancet* 1999 Oct 2;354(9185):1191-9.

3. WHO. Report of the Consultative Meeting on Cutaneous Leishmaniais. Geneva: WHO; 2007.

4. Brasil. Ministério da Saúde. Manual de Vigilância da Leishmaniose Tegumentar Americana. 2nd ed. Brasília (DF);2007.

5. Lainson R. The American leishmaniases: some observations on their ecology and epidemiology. *Trans R Soc Trop Med Hyg*. 1983;77(5):569-96.

6. Rath S, Trivelin LA, Imbrunito TR, Tomazela DM, Jesús MN, Marzal PC. Antimoniais empregados no tratamento da leishmaniose: estado da arte. Quim Nova. 2003;26(4):550-555.

7. Goodman and Gilman's. The pharmacological basis of therapeutics. 11th ed. New York: The McGraw-Hill Companies; 2006.

8. Berman JD**.** Chemoterapy *for* leishmaniasis: biochemical mechanismis, clinical efficacy, and future strategies. *Rev Infect Dis*. 1988 May-Jun;10(3):560-86.

9. Lima EB, Porto C, Motta JOC, Sampaio RNR. Tratamento da leishmaniose tegumentar americana. *An Bras Dermatol*. 2007; 82(2):111-24.

10. Oliveira-Neto MP, Mattos M, Pirmez C, Fernandes O, Gonçalves-Costa SC, Souza CF, et al. Mucosal leishmaniasis ("espundia") responsive to low dose of N-methyl glucamine (Glucantime) in Rio de Janeiro, Brazil. *Rev Inst Med Trop Sao Paulo*. 2000; 42:321-325.

11. Oliveira-Neto MP, Schubach A, Araujo ML, Pirmez C. High and low doses of antimony (Sb^v) in American cutaneous leishmaniasis. A five years follow-up study of 15 patients. *Mem Inst Oswaldo Cruz*. 1996; 91:207-209.

12. Arevalo I, Tulliano G, Quispe A, Spaeth G, Matlashewski G, Llanos-Cuentas A, Pollack H. Role of imiquimod and parenteral meglumine antimoniate in the initial treatment of cutaneous leishmaniasis. *Clin Infect Dis*. 2007 Jun 15;44(12):1549.

13. Martinez S, Gonzalez M, Vernaza ME. Treatment of cutaneous leishmaniasis with allopurinol and stibogluconate. *Clin Infect Dis*. 1997 Feb;24(2):165-9.

14. Arana BA, Navin TR, Arana FE, Berman JD, Rosenkaimer F. Efficacy of a short course (10 days) of high-dose meglumine antimonate with or without interferon-gamma in treating cutaneous leishmaniasis in Guatemala. *Clin Infect Dis*. 1994 Mar;18(3):381-4.

15. Khatami A, Firooz A, Gorouhi F, Dowlati Y. Treatment of acute Old World cutaneous leishmaniasis: A systematic review of the randomized controlled trials. *J Am Acad Dermatol.* 2007;57(2):335-356

16. Kane-Gill S, Rea RS, Verrico MM, Weber RJ. Adverse-drug- event rates for high-cost and high-use drugs in the intensive care unit. Am J Health Syst Pharm. 2006 Oct 1;63(19):1876-81.

17. Deeks JJ, Higgins, JPT, Altman DG, editors. Including Adverse effects. In: Higgins JPT, Green S, editors. Cochrane Handbook for Systematic Reviews of Interventions 4.2.6 [updated September 2006]; Appendix 6b. The Cochrane Library, Issue 4, 2006. Chichester, UK: John Wiley & Sons, Ltd.

18. Capellá D, Laporte JR. Mecanismos de produção e diagnóstico clínico dos efeitos indesejáveis produzidos por medicamentos. In: Laporte JR, Tognoni G, Rozenfeld S. Epidemiologia do medicamento. São Paulo-Rio de janeiro: Hucitec-Abrasco, 115-124, 1989.

19. Loke Y K, Price D, Herxheimer A. Systematic reviews of adverse effects: framework for a structural approach. *BMC Med Res Methodol.* 2007;7:32. http://www.biomedcenter.com/1471-2288/7/32 (accessed Apr 23, 2008).

20. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human use. ICH Harmonised Tripartite Guideline. Guideline for Good Clinical Practice (GCP) E6(R1) Version 10. [cited june 1996]. http://www.ich.org/LOB/media/MEDIA482.pdf

21. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human use. Clinical Safety Data Management: Definitions and Standards for Expedited Reporting E2A (ICH E2A). [cited 1994 Oct 27]. http://www.ich.org/cache/ compo/276-254-1.html.

22. Sutton, J. A.; Abranms, R.K.; Jones, R.D.; Sheldon, A.T.; Song, F. Methods for Meta-Analysis in Medical Research: Leicester: Wiley e Sons, LTDA, 2000.

23. Vieira S, Hossne WS. Metodologia Científica para Análise de Saúde, São Paulo: Campus, 2001. p 135-153.

24. Egger M, Smith GD, Altman DG. *Systematic Reviews in Health Care: Meta-analysis in context.* Londres: BMJ Publishing group. 2nd ed, 2001.

25. Pai M., McCulloch M., Gorman, JD *et al.* Systematic reviews and meta-analyses: an illustrated, step-by-step guide. *Nat Med J India*. 2004; 17(2).

26. Tuon FF, Amato VS, Graf MS, Siqueira AM, Nicodemo AC, Amato Neto V. Treatment of New World cutaneous leishmaniasis – a systematic review with a meta-analysis. *Int J Dermatol*. 2008 Feb;47(2):109-124.

27. Gonzáles U, Pinart M, Reginfo-Pardo M, Macaya A, Alvar J, Tweed JA. Interventions for American cutaneous and mucocutaneous leishmaniasis. *Cochrane Database Syst Rev*. 2009 Apr 15;(2):CD004834.