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Pharmacoepidemiology and thalidomide embryopathy surveillance in Brazil

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ABSTRACT

Introduction: Thalidomide causes congenital defects in children, such as limb reduction defects. Currently, it is used for a few indications; in Brazil, where leprosy is endemic, thalidomide is used for the treatment of erythema nodosum leprosum, and recent cases of thalidomide embryopathy have been reported.
Methods: We analyzed the frequency of births with phenotypes consistent with thalidomide embryopathy (TEP) and correlated this with the distribution of thalidomide and the prevalence of leprosy between 2005 and 2010 in Brazil.
Results: A total of 5,889,210 thalidomide tablets were distributed; the prevalence of limb reduction defects was 1.60 (CI95%: 1.54–1.66) and TEP was 0.11 (CI95%: 0.10–0.13) per 10,000 births. Poisson regression showed an increase in cases of TEP and limb reduction defects per 100,000 tablets dispensed. Clusters and geographical isolates were identified in several regions.
Conclusions: There is a correlation between thalidomide and TEP showing that thalidomide embryopathy should be monitored in countries where this medication is available.

1. Introduction

Thalidomide is a drug that was first synthesized in 1954 in West Germany and was first marketed in 1956 [1,2]. It was successfully marketed as a sedative and was soon licensed in over 46 countries. However, it was withdrawn from the market in the early 1960s because the relationship between thalidomide treatment and birth defects that had been observed could no longer be negated by pharmaceutical companies and skeptics among health care professionals; at least 10,000 children were born with congenital defects resulting from intrauterine exposure to the drug [1,2].

Clinical use of thalidomide would have ceased if it were not for the discovery of its efficacy in the treatment of erythema nodosum leprosum, an inflammatory condition that is common in leprosy patients [3]. Approximately, 30–50% of individuals who have lepromatous leprosy in its most severe form develop erythema nodosum leprosum, which has important implications for the physical disabilities of the patient with leprosy [4,5]. Thalidomide is an effective treatment option for erythema nodosum leprosum because of its anti-inflammatory, immunomodulatory, and antiangiogenic properties [6–8]. Additionally, as a result of these properties, thalidomide has also been used to treat several other diseases – especially, the complications from AIDS, cancer, and autoimmune diseases – in many countries since the late 1990s [9].

Thalidomide has been available in Brazil since it was first marketed in 1958. In 1963, it was withdrawn from the market because of its teratogenic effect [10]; however, by 1965, it was already being used to treat erythema nodosum leprosum [11]. Today, thalidomide is the drug of choice for the treatment of erythema nodosum leprosum in Brazil, except for women of childbearing age [12–15]. This

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drug has become a widely used medication because of the high prevalence of the disease in the country – currently some areas have more than 8 cases per 10,000 inhabitants [15].

Currently, Brazil has strict legislation that restricts the use and distribution of thalidomide [13,14]. The drug is not commercially marketed and is only distributed by special government programs for the treatment of erythema nodosum leprosum, lupus erythematosus, graft-versus-host disease, idiopathic ulceration resulting from AIDS, and multiple myeloma. Additionally, when the drug is prescribed to women of childbearing age, two contraceptive methods are recommended, and pregnancy tests are required prior to use. However, the regulations were less rigorous before these recommendations came into effect, which led to the birth of children affected by thalidomide embryopathy [10,16].

In 1996, there were 33 new published cases of people afflicted with birth defects caused by thalidomide, who were born after 1970 [16]. In 2007, three more live births were identified [17]. The emergence of these cases was attributed to the endemicity of leprosy and the lack of supervision in the distribution and use of thalidomide.

For this reason, in a previous study, a thalidomide embryopathy phenotype (TEP) was defined (as the presence of intercalary and preaxial bilateral limb defects) and used as the basis of a screening program. In a one-year pilot test, the screening method proved to be both sensitive and feasible, but the work was limited to births occurring in only a few hospitals around the country, and hence, does not represent every region in the country [18]. Thus, in the work presented here, we apply the same surveillance method to all births in Brazil between 2005 and 2010. We also accessed the leprosy prevalence data and information concerning the distribution of thalidomide for the same period and compared these three variables in order to identify unusual groupings of limb reduction defects that correspond with the occurrence of thalidomide embryopathy in areas with high thalidomide use.

2. Method

2.1. Source of the data

For the study, we accessed the records of all births between 2005 and 2010 and used Birth Certificates to compile the relevant information about demographics and details of the birth [19]. Birth certificates contains a field for entry of a description of any congenital malformations, which were later defined in accordance with the tenth revision of the international classification of diseases (ICD-10). It is possible that in using the ICD classification some anomalies are misclassified; however, since there are about 3 million births per year in Brazil, individual examination of every case is unfeasible.

Almost every organ can be affected after exposure to thalidomide; limbs are the most commonly affected, followed by eye and ear malformation, and cardiac anomalies [1,2,20]. In some cohorts, around 60–90% of those affected by embryopathy had limb reduction defects [21,22]. Because of its high frequency, the surveillance phenotype used was based on the occurrence of limb reduction defects characteristic of thalidomide embryopathy, as used in our previous study [18]. Limb reduction defects are characterized by the total or partial absence, or severe hypoplasia, of limb skeletal structures [23]. The limb malformations that are typically observed in thalidomide embryopathy are intercalary and preaxial bilateral defects and are not associated with known genetic syndromes [1,2,24]. This surveillance phenotype was designated as TEP.

We first selected all the recorded births with limb reduction defects with an ICD classification of Q71-Q73 (upper, lower, and non-specified limb reduction defects). In accordance with the definition of TEP, this data set was then reduced to include only births with any of the following defects: Q71.1, congenital absence of arm and forearm, with hand being present; Q71.4, longitudinal reduction of the radius; Q72.1, congenital absence of the thigh and leg with foot being present; Q72.4, longitudinal reduction of the tibia; Q73.1, phocomelia, limb(s) not specified.

The data for leprosy prevalence by state was directly supplied by the National Leprosy Program from the Health Surveillance Secretary of the Brazilian Ministry of Health. Leprosy is a condition with compulsory notification in Brazil; for each new case diagnosed there is a notification from the home state, and this information is deposited in the "Notifiable Diseases Information System" (SINAN), which gathers national information regarding notifiable diseases [25]. Information concerning the distribution of thalidomide has been available since 2003 – when regulations came into force in Brazil – and describes the use of the drug on both a per state and a per disease basis (13). In this study, only general information about the dispensation of thalidomide (i.e. the state of use and the disease treated) was considered.

2.2. Statistical analyses

Poisson regression analysis was used to assess the relationship between the number of tablets distributed per state and the number of TEP/limb reduction defect cases. Since the occurrence of TEP and that of limb reduction defects are not identical, they were analyzed separately across the entirety of Brazil across the whole time period covered. A value of $p < 0.05$ was considered significant. The analyses were conducted using SPSS software (v 20.01).

To analyze the TEP distribution data, the Cluster and Outlier analysis (Anselin Local Moran's I) tool present in the ArcGIS® geoprocessing software (v. 9.0) was used. This analysis identifies spatial clusters of features with similar attribute values. The program calculates the local value of Moran's *I*, a *z*-score, *p*-value, and a code that represents the type of cluster for each resource. The *z*-scores and *p*-values represent the statistical significance. Thus, it is possible to identify two types of clusters: positive *I* values indicate that a geographical location is surrounded by similar TEP values; thus, it becomes a cluster; conversely, negative *I* values indicate that the location is surrounded by different TEP values; hence, this is considered an outlier. For more details about cluster and outlier analyses, refer to Moore and Carpenter, 1999 [26].

2.3. Ethics statement

All data used in this study is public and not personally identifiable and as such, its use does not require ethical approval.

Data of leprosy prevalence and distribution of thalidomide are available as absolute numbers, with the state of origin identified. Limb reduction defects are coded according to ICD-10 per municipality, and researchers only had access to these codes and the municipalities of occurrence. The data is available on the websites of the Brazilian government (http://dtr2004.saude.gov.br/sinanweb/tabnet/dh?sinannet/hanseniase/bases/Hansbrnet.def, and http://tabnet.datasus.gov.br/cgi/deftohtm.exe?SINASC/cnv/nvuf.def).

Research in Brazil is regulated by the Resolution of the National Health Council (CNS) 466/2012 [27], and these regulations apply to research involving humans. Research using public databases and non-personally identifiable data does not require ethical appraisal in Brazil.

3. Results

From 2005 to 2010, 5,889,210 thalidomide tablets were distributed, with the state of São Paulo having the highest dispensation rate, followed by Minas Gerais and Rio de Janeiro (Table 1). In this period, there were 17,544,772 births in Brazil. Among these, there

Table 1
Distribution of thalidomide use, limb reduction defects leprosy, and population during the years 2005–2010 in Brazil, per state.

State	Thalidomide[a]	Population[b]	Births	LRD	LRD Prev.	TEP	TEP Prev.	Leprosy[c]
SÃO PAULO	1,186,200	246,820,072	3,619,542	651	1.80	44	0.122	0.53
MINAS GERAIS	639,840	117,917,451	1,571,472	256	1.63	12	0.076	1.20
RIO DE JANEIRO	502,080	94,556,355	1,304,715	257	1.97	16	0.123	1.43
PARANA	418,560	62,882,104	913,804	181	1.98	14	0.153	1.19
CEARA	336,480	50,100,937	802,776	85	1.06	8	0.100	3.04
MATO GROSSO	270,720	17,565,130	296,396	54	1.82	6	0.202	11.10
PERNAMBUCO	246,720	51,848,031	864,809	191	2.21	18	0.208	3.41
BAHIA	245,760	850,06,137	1,323,137	138	1.04	4	0.030	2.25
GOIAS	238,080	34,966,423	526,587	96	1.82	4	0.076	5.17
RONDONIA	222,720	9,246,903	154,705	23	1.49	2	0.129	6.53
DISTRITO FEDERAL	209,790	14,885,128	267,512	31	1.16	4	0.150	1.16
ESPIRITO SANTO	194,400	20,848,046	309,992	35	1.13	0	0.000	2.89
PIAUI	124,800	18,491,866	318,300	31	0.97	3	0.094	5.38
MATO GROSSO DO SUL	118,560	14,039,358	240,953	36	1.49	4	0.166	2.49
MARANHAO	116,370	37,800,422	756,500	110	1.45	5	0.066	7.15
SANTA CATARINA	105,120	36,293,886	503,885	96	1.91	9	0.179	0.32
AMAZONAS	98,400	20,150,884	447,185	54	1.21	3	0.067	2.83
PARAIBA	85,920	22,148,315	364,659	34	0.93	2	0.055	2.25
PARA	84,480	43,663,822	880,201	136	1.55	6	0.068	6.45
RIO GRANDE DO NORTE	82,560	18,542,989	294,858	53	1.80	7	0.237	1.20
RIO GRANDE DO SUL	79,920	65,351,720	823,965	138	1.67	18	0.218	0.18
TOCANTINS	77,760	7,953,057	152,504	20	1.31	0	0.000	7.88
ALAGOAS	65,730	18,555,755	343,009	30	0.87	2	0.058	1.33
SERGIPE	56,640	12,089,162	215,989	42	1.94	0	0.000	2.28
RORAIMA	43,200	2,494,698	58,350	10	1.71	0	0.000	7.80
ACRE	22,080	4,164,635	101,351	6	0.59	1	0.099	3.40
AMAPA	16,320	3,756,250	87,616	8	0.91	0	0.000	3.41
TOTAL	5,889,210	1,132,139,536	17,544,772	2802	1.60*	192	0.11*	3.49*

[a] Number of thalidomide tablets dispensed.
[b] Population in years 2005–2010.
[c] Leprosy prevalence per 10,000 inhabitants.
* Average; LRD, limb reduction defects; LRD Prev., limb reduction defect prevalence; TEP, thalidomide embryopathy phenotype; TEP Prev., thalidomide embryopathy phenotype prevalence.

were 2802 limb reduction defects recorded, with an overall prevalence of 1.6 for every 10,000 births. There were 192 limb reduction defects classified as TEP, with an overall prevalence of 0.11 per 10,000 births.

The dispensing of thalidomide was proportional to the population size in the three most populous states in Brazil (Sao Paulo, Rio de Janeiro, and Minas Gerais). Most of the tablets were used to treat erythema nodosum leprosum (63%). Lupus treatment was responsible for the use of 33% of the tablets, and AIDS-related conditions were responsible for the remaining 4% (data not shown).

The states with the highest prevalence of LRDs were Pernambuco, Paraná, and Rio de Janeiro, while those with the highest frequency of TEP were Rio Grande do Norte, Rio Grande do Sul, and Pernambuco (Fig. 1). The prevalence of leprosy is concentrated in the north, center-west, and northeast regions, with the highest rates ranging from 8 to 11 cases per 10,000 inhabitants.

Poisson regression analysis showed a significant direct correlation between the absolute number of thalidomide tablets dispensed and the occurrence of limb reduction defects and TEP (Table 2). We observed that for every 100,000 thalidomide tablets dispensed, there is a 27.9% increase in cases of limb reduction defects (Table 2). Likewise, a similar result was observed for TEP, in which for every 100,000 tablets dispensed, an increase of 26.1% cases of thalidomide embryopathy was observed. The association between thalidomide distribution and leprosy prevalence was not statistically significant (data not shown).

Table 2
Poisson regression analysis using the number of thalidomide tablets prescribed, occurrence of limb reduction defects, and thalidomide embryopathy phenotype.

	Thalidomide (100,000 tablets)		
	Exp(β)	CI95%	*p*
LRD	1.279	1.268;1.290	<0.001
TEP	1.261	1.220;1.304	<0.001

LRD, limb reduction defects; TEP, thalidomide embryopathy phenotype.

In the cluster and outlier analyses, we observed that the TEP clusters were mainly concentrated in the south and southeast of Brazil, with a few in the north and northeastern region of Brazil. The isolates were scattered across all regions, except for the north (Fig. 1).

4. Discussion

In this paper we examined the three most important variables for the epidemiological evaluation of the occurrence of thalidomide embryopathy: distribution of drug dispensation, prevalence of the main target disease treated by this drug, and characteristics of TEP, at the population level. The use of thalidomide is an extremely important issue in Brazil because it is a country that continues to report cases of thalidomide embryopathy among newborn babies [16,17,20]. However, this problem might not be limited to our country. Data shown in this work include a period of time in which the medication became widely available – both in Brazil and worldwide – for the treatment of various clinical conditions; additionally, its use is not limited to erythema nodosum leprosum, as shown by the growing number of clinical trials and citations in scientific databases in recent years [9,28].

The period from 2005 to 2010 was chosen for this study because of the fact that, since 2003, specific legislation has been implemented to regulate the prescription and dispensation of thalidomide in Brazil [13]. The recording of birth defects on birth certificates has been mandatory since 1999, and data from this source has already been used in other studies to evaluate congenital defects [29–31]. Luquetti et al. showed that the use of

Fig. 1. Cluster analysis of the prevalence of thalidomide embryopathy phenotype (TEP) in Brazil between 2005 and 2010. *Footnote*: Black circles: Statistically significant cluster with a high positive *z*-score, tending to 2; blue circles: Isolates (areas with high prevalence surrounded by areas with a low prevalence) have a high *z*-score negative, tending to −2; color gradient: concentrations of cases of TEP (thalidomide embryopathy phenotype–from green (lower concentration) to red (higher concentrations).

Birth Certificates allows for the specific detection of congenital defects, albeit with varying sensitivity and a substantial rate of underdiagnosis. Another important question that might be raised is the coding of the defects by ICD-10. One cannot exclude the errors between the original description by the physician and the coding used on the certificate at the time of registration. Moreover, the sensitivity of the recording of congenital defects will vary across the different regions of Brazil. Regions such as the south and southeast have high rates of defects, while the north, northeast, and center-west show low prevalence. This may be because of the fact that the south and southeast regions have a higher number of tertiary hospitals and generally have more effective public health infrastructure, including better-trained personnel registering congenital defects. Previous work has shown differences in birth defect registration between different regions of the country, and this was also observed here [30].

Since there was a large difference in the type of data available from different states, in this study, we only analyzed data with absolute numbers. Another reason to evaluate absolute numbers of dispensation of thalidomide, regardless of the sex and age of the user, is that medicine sharing is a common practice in Brazil; it even has been reported in one case of thalidomide embryopathy [17]. We are aware that this is an important limitation; however, these are the only data available for this type of analyses. Nevertheless, our study showed a direct correlation between the number of thalidomide tablets dispensed by state and the number of children born with the phenotype typical of thalidomide embryopathy. This association between absolute numbers indicates that many cases

may be occurring within the identified clusters. Therefore, to verify this relationship, long-term defect rates should be investigated, and careful recording of birth defects should be ensured at-risk areas.

Furthermore, we detected clusters and geographical isolates of TEP cases in several areas of the country. The clusters corresponded to the most populous regions and areas where the occurrence of birth defects is better recorded. The isolates represent thalidomide embryopathy frequency peaks that differ from what was recorded in the immediate vicinity. One of these isolates (Maranhao) is an area in which our group had previously identified cases of thalidomide embryopathy [27]. This shows that our analysis by geographic systems enables the accurate identification of locations that require public health intervention.

It is important to mention that the occurrence of TEP does not necessarily mean that the individual has thalidomide embryopathy. There are other syndromes such as Holt–Oram syndrome, Roberts SC syndrome, Fanconi anemia, Okihiro syndrome, femur-fibula-ulna (FFU) syndrome, and Cornelia de Lange syndrome, among others [2,24]. The Brazilian thalidomide cases also offer an opportunity to study affected patients throughout their lives to determine if other late onset or physiological damage is apparent, but also to determine the full range of damage this drug can cause. Birth certificates will only record the outward/obvious damage at birth and not internal, physiological or late onset damage (that may only present in later childhood or even adulthood). This more accurate clinical evaluation in affected by thalidomide embryopathy throughout their life can reveal findings, like conditions anticipated or caused by thalidomide exposure, which had not been identified at birth. This approach could help in the diagnosis and care for these conditions (if any) as well as to provide insights about teratogenesis mechanisms. However, in this nationwide epidemiological study, our objective was not to perform specific diagnoses or clinical evaluations, but to generate hypotheses that serve as a first step toward the initiation of emergency educational measures for safe use of the drug. Unfortunately, we have no data regarding the dispensation of medication and prevalence of birth defects in previous years and therefore, cannot carry out an analogous study across other timeframes. From the data presented here, it was possible to devise and conduct an effective surveillance over a national population. It is important to note that a single case of thalidomide embryopathy may be regarded as an epidemic since they are all avoidable through pregnancy prevention and education programs.

In conclusion, the relationship between the variables examined in this paper is concerning considering the number of tablets dispensed and the fact that a single tablet of thalidomide can cause congenital defects. Furthermore, the data presented here indicate that the increased availability of thalidomide in Brazil is related to a higher frequency of defects that are characteristic of thalidomide embryopathy, regardless of the therapeutic indication for which the thalidomide was dispensed. These results raise important questions for public health policies considering that the prescription of thalidomide is expanding worldwide.

Conflict of interest

The authors declare that there are no conflicts of interest.

Transparency document

The Transparency document associated with this article can be found in the online version.

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