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Second-Line Injectable Drugs for the Treatment of Multidrug-Resistant Tuberculosis. Why do We Keep Using Them?

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Abstract

Second-line injectable drugs (kanamycin, amikacin and capreomycin) have been an integral part of the multidrug-resistant tuberculosis (MDR-TB) treatment regimen for decades, despite their known association with renal failure and ototoxicity. Unfortunately, there are many countries that haven't included new or reused drugs in their treatment regimens for MDR-TB and still depend on second-line injectable drugs (SLIDs) in order to have a sufficient amount of effective drugs in their regimens. Our purpose is to show the frequency and severity of the ototoxicity associated with the use of SLIDs only detected initially by means of an audiometry. We conducted a retrospective analysis including all the patients who received treatment regimens with SLIDs from 2010 to 2017 in a tuberculosis clinic in Mexico. 47 patients who received SLIDs (amikacin, kanamycin, capreomycin) were included in the analysis. The mean age was 40.3 ± 16.4 years. Thirty one patients (63.3%) had previously received TB treatment in the past. The most commonly used SLID was amikacin in 33 cases (67.3%), followed by capreomycin in 14 cases (28.6%). Twenty seven patients (55.1%) developed significant hearing loss (> 40 dB), and 13 patients (26.5%) developed severe or profound hearing loss (> 70 dB). Severe hearing loss is a common, irreversible and now unnecessary complication of the MDR/RR-TB (multidrug- and rifampicin-resistant tuberculosis) treatment, since the SLIDs may and shall be substituted by new and reused, more effective and far less toxic drugs.

Key words: Tuberculosis, Multidrug-Resistant, Second-line injectables, Ototoxicity

Introduction

Second-line injectable drugs (kanamycin, amikacin and capreomycin) have been an essential part of the multidrug-resistant tuberculosis (MDR-TB) treatment regimen for decades, despite their known nephrotoxicity and ototoxicity[1].

Now, a recent statement of the World Health Organization (WHO) questions the efficacy of the SLIDs and even removes kanamycin and capreomycin from the list of essential drugs, leaving amikacin as an option only in cases when its use can't be avoided due to lack of access or intolerance to more effective and less toxic drugs[2].

Unfortunately, many countries are not including new drugs, such as bedaquiline and delamanid (or linezolid and clofazimine) in their treatment regimens for MDR-TB and still depend on second-line injectable drugs (SLIDs) in order to constitute their MDR-TB regimens. Even more serious, access to an audiometry is rarely available during treatment with SLIDs, despite the well-known fact that clinical

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detection of hearing loss has extremely low sensitivity[3] and the recommendation to perform periodic audiometries during follow-up while the patient is receiving SLIDs.

Our purpose is to show the frequency and severity of the ototoxicity associated with the use of SLIDs, only detected by an audiometry in a specialized MDR-TB treatment clinic.

Materials and Methods

We carried out a retrospective review of the 2010-2017 files in the Tuberculosis Clinic of the Hospital General de Tijuana. The city of Tijuana, located in the Northwest of Mexico, has the highest TB rate in the country (60 cases per 10^5 inhabitants) and a high rate of MDR-TB (3.9 cases per 10^5)[4]. All the patients who received treatment regimens with a SLID were included.

In addition to demographic variables, we obtained data on the number of previous TB treatments, culture-based resistance profiles, the type of SLID that was used, the daily SLID dose (administered 5 days a week), the total number of SLID doses that were received, culture conversion time, reasons for suspending the SLID and initial and final results of creatinine, blood urea nitrogen (BUN) and audiometries.

The pure tone audiometry (AMCO Electronics, Tustin®, CA, USA) was carried out at the beginning of the study, every two months and at the end of the injectable phase.

Ototoxicity was classified according to the range of hearing loss in decibels (dB), as moderate (41-55 dB), moderately severe (56-70 dB), severe (71-90 dB) and profound (($\geq$ 91 dB)[5].

Statistical Analysis

The statistical analysis was performed with a commercial statistical package (SPSS®24, IBM, Armonk, New York). The paired t test (tests performed at baseline and after administration of the SLIDs) was used for the comparisons between creatinine and blood urea nitrogen tests and audiometries.

The study was authorized by the Hospital's Ethics Committee (NATIONAL COMMISSION OF BIOETHICS [CONBIOÉTICA]-02-COMMITTEE FOR ETHICAL RESEARCH [CEI]-001-20170526). Since it was an anonymous review of the files, the Committee considered that a written informed consent was not necessary.

Results

We reviewed the records of 47 patients who received SLIDs. Their mean age was 40.3 ± 16.4 years (range: 15-76 years). Twenty-nine patients (61.7%) were male. The most common comorbility was diabetes mellitus in 16 patients (34%), followed by hypertension (4 patients, 8.5%) and HIV/AIDS (3 patients, 6.4%). The SLID was included in the regimen of 37 patients with a strain of MDR/RR-TB (75.5%); the rest of the patients received one SLID due to poly-resistant tuberculosis or because of the presence of adverse reactions to first-line drugs.

Thirty one patients (66%) had received TB treatment in the past, an average of one treatment (1.0 ± 1.0), with a range of 1 to 4 treatments.

The most commonly used SLID was amikacin in 33 cases (70.2%), followed by capreomycin in 14 cases (29.7%). Kanamycin was used in 2 cases (4.2%). The patients received 135.4 ± 54.2 doses of injectable drugs (range of 32-277); the mean dose was 907.1 ± 143.9 mg (range of 500-1,000 mg). Time to culture conversion was 83.8 ± 58.7 days.

The injectable drug was suspended in 33 cases (70.2%) due to culture conversion, in 7 cases (14.8%) because of renal failure, in 4 cases (8.4%) due to hearing loss detected by audiometry, and in 2 cases (4.2%) for vestibular symptoms.

Basal creatinine was 0.72 ± 0.19 mg/dL, and final creatinine was 1.15 ± 1.5 mg/dL ($p = 0.56$); basal BUN was 11.4 ± 4.2 mg/dL and final BUN was 15.6 ± 8.8 mg/dL ($p = 0.001$). All the renal function values, though slightly increased, were still within normal ranges.

Twenty six patients (55.3%) developed significant hearing loss (> 40 dB), and 13 patients (27.7%) developed severe or profound hearing loss **(Table 1)**.

TABLE 1. Degree of Hypoacusia Secondary to the Use of SLIDs

Degree of hypoacusia in decibels (dB)	N° of patients (%)	Masculine gender (%)	Form of presentation	Number of doses (average and range)
Moderate (41-55 dB)	7 (14.8%)	(85.7%)	Pulmonary	89.8 (32-174)
Moderately severe (56-70 dB)	8 (17%)	(62.5%)	Pulmonary	158.6 (116-227)
Severe (71-90 dB)	9 (19.1%)	(100%)	Pulmonary	118.7 (62-212)
Very severe (≥ 91 dB)	1 (2.12%)	(0%)	Pulmonary	47

Discussion

It is very difficult to quantify the impact of a reduction in auditory acuity upon the quality of life of a person and his/her capacity to lead a productive life, even when he/she is cured of MDR-TB[6].

Our data show that, though clinically unnoticeable, up to one every four patients treated with SLIDs will develop significant hearing loss. This fact was even more evident in patients who, due to their age, had already experienced some degree of presbyacusia. In some cases, it was necessary to keep using the SLID despite the hearing impairment due to the lack of culture conversion and for not having other effective drugs to replace it.

Renal function impairment induced by aminoglycosides is usually reversible, and ototoxic damage is permanent and irreversible, and may occur even with the administration of several doses to genetically predisposed individuals[7, 8].

Hearing loss caused by aminoglycosides is associated with the selective destruction of the ciliated cells of the cochlea, initially in those that detect high frequency sounds and gradually surpass the low frequency ones. That is why neither the patient nor his/her doctor can initially detect the damage unless they perform routine audiometry tests[6]. Unfortunately, in the countries with the highest burden of MDR-TB (and, thus with greater use of SLIDs), both the audiometry equipment and the personnel trained for monitoring hearing loss are rarely available[9].

Why do we keep using SLIDs for the treatment of MDR/RR-TB even now when we have new, more effective, and less toxic drugs? To begin with, international guidelines have recommended the SLIDs as a pillar of the MDR/RR-TB treatment for many years[10]. Fortunately, the WHO has recently published a fast communication regarding the changes in treatment regimens for MDR/RR-TB, which include new and reused drugs for a fully oral regimen; kanamycin and capreomycin are no longer recommended due to a higher risk of treatment failure and relapse in MDR/RR-TB regimens, and the use of amikacin is recommended only to complete treatment regimens when other oral, more effective and less toxic drugs can't be administered[2]. Secondly, the cost of these new drugs is much higher in comparison with older drugs. However, as an equity principle, every patient with MDR/RR-TB must have access to the most effective and safe treatment available at present[11]. The National Tuberculosis Programs (NTPs) must be funded by the governments in order to strengthen their activities; in this specific case, for the diagnosis and treatment of MDR/RR-TB (besides the external funds received by developing countries from the Global Fund)[12, 13].

The WHO acknowledges it will not be possible to immediately adhere to the new standards of care in each country and in each individual patient with MDR-TB, but the countries shall begin their strategic planning right away in order to allow for a rapid transition to new international guidelines[2].

Conclusion

Severe hearing loss is a common, irreversible and now unnecessary complication of the MDR/RR-TB treatment, since the SLID may and shall be substituted by more effective and far less toxic drugs in accordance with international recommendations.

Conflicts of interest: The study did not receive any funds and there are no conflicts of interest to declare.

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