

Prescription patterns of riluzole in a population of patients with motor neuron disease

Patrón de prescripción de riluzol en una población de pacientes con enfermedad de neurona motora.

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SUMMARY

OBJECTIVE: To determine the prescription pattern of riluzol and the variables associated to its use in a population of patients with motor neuron disease affiliated to the Colombian General Social Security Health System (SGSSS) in 2017.

METHOD: Descriptive cross-sectional study. Through a systemized data base of approximately 3,5 million members to the Colombian SGSSS; patients who had been given riluzol uninterruptedly between April 1 and June 30 of 2017, were selected. Sociodemographic, pharmacological variables and comorbidities were analyzed. Defined daily dose (DDD) was estimated for 1.000 inhabitants/day and its costs.

RESULTS: There were found 81 patients with motor neuron disease receiving riluzol, with an average age of $60,8 \pm 12,6$ years. 48.1% were male. The prevalence of motor neuron disease was 29/100.000 individuals. Patients received riluzol in 50 mg tablets and the doses was estimated in 0,016 DDD for 1.000 inhabitants/day. 63% were receiving medicines that reflect comorbidity or could interact with riluzol. The total cost of riluzol dispensed in 2017 was USD 85.348 and per prescribed daily dose on average was USD 2,3.

CONCLUSIONS: The use of riluzol in patients with motor neuron disease in Colombia was carried by the recommended doses by the WHO and with a direct cost lower than reported in other countries. Studies are recommended in order to determine the effectiveness of riluzol in real-life conditions.

KEYWORDS: Amyotrophic Lateral Sclerosis; Motor Neuron Disease; Riluzole; Drug Prescriptions; Drug Utilization; Pharmacoepidemiology (MeSH).

RESUMEN

OBJETIVOS: Determinar el patrón de prescripción de riluzol y las variables asociadas a su utilización en una población de pacientes con enfermedad de neurona motora afiliados al Sistema General de Seguridad Social en Salud de Colombia (SGSSS) en 2017.

METODOLOGÍA: Estudio descriptivo de corte transversal. Mediante una base de datos sistematizada de aproximadamente 3,5 millones de afiliados al SGSSS de Colombia; se seleccionaron pacientes a quienes se les haya dispensado riluzol de manera ininterrumpida entre 1 abril y 30 junio de 2017. Se analizaron variables socio-demográficas, farmacológicas y las comorbilidades. Se estimaron la dosis diaria definida (DDD) por 1.000 habitantes/día y los costos.

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RESULTADOS: Se encontraron 81 pacientes con enfermedad de neurona motora recibiendo riluzol, con edad promedio de $60,8 \pm 12,6$ años. El 48,1% eran hombres. La prevalencia de enfermedad de neurona motora fue 2,29/100.000 personas. Los pacientes recibieron riluzol en tabletas de 50 mg y se estimó la dosis en 0,016 DDD por 1.000 habitantes/día. El 63% recibían medicamentos que reflejan comorbilidad o pudieran tener interacción con riluzol. El costo total del riluzol dispensado en 2017 fue USD 85.348 y por dosis diaria prescrita en promedio fue USD 2,3.

CONCLUSIONES: El uso de riluzol en pacientes con enfermedad de neurona motora en Colombia se realizó a las dosis recomendadas por la OMS y con un costo directo menor al reportado en otros países. Se recomienda realizar estudios que permitan determinar la efectividad del riluzol en condiciones de la vida real.

PALABRAS CLAVE: Enfermedad de neurona motora, Riluzol, Prescripciones de Medicamentos, Utilización de Medicamentos, Farmacoepidemiología, Colombia (DeCS).

INTRODUCTION

Amyotrophic lateral sclerosis (ALS) is characterized by progressive degeneration of the upper (UMN) and lower motor neurons (LMN), causing weakness, fatigue and muscular atrophy (1,2). Four main phenotypes of motor neuron disease have been described: classic ALS, progressive bulbar palsy, primary lateral sclerosis and progressive muscular atrophy (1,3). It leads to death due to respiratory failure an average of 3 to 5 years after the onset of symptoms (4).

Epidemiological studies show variability among populations. A systematic literature review on the global epidemiology of ALS reported an average incidence in Europe of 2.08 cases/100,000 persons per year and an estimated average prevalence of 5.4 cases/100,000 persons (5). In the United States, the average incidence was 1.75/100,000 and the prevalence was 3.4/100,000(5). A study conducted in Uruguay showed an incidence of 1.4/100,000 people per year and a prevalence of 1.9/100,000(6). Point prevalence of ALS in Antioquia, Colombia in December 2014 was estimated at 4.9/100,000 (95% CI 2.0-7.8), and the incidence was estimated at 1.4/100,000/year (95% CI 0.5-2.2) using capture-recapture method (7). Some studies have shown a slightly higher incidence in men (2,5,8).

In 1995, the FDA approved riluzole as a neuroprotective and disease-modifying agent, demonstrating a 3- to 6-month increase in survival in two large clinical trials (9-11). The annual direct cost of the medication per patient in developed countries such as Germany, Canada and the United States is reported between \$ 3,000 to \$ 15,000 (12-14). The Colombian Healthcare System offers universal coverage through two regimes, one paid by employers and workers; and another subsidized by the state, and has a benefit plan that does not include riluzole. However, affiliated patients can access it through special requests made by physicians. In this context and given that there are no studies on its use in Colombia, the authors intended to determine the prescription profile of riluzole and the variables associated with its use in a population of patients with motor neuron

disease. In addition, due to the differences in the cost of use reported among developed countries, the authors estimated the economic impact of its prescription.

MATERIALS AND METHODS

A cross-sectional study was conducted on the prescription profile of riluzole in patients with motor neuron disease in a population of approximately 3.5 million people enrolled in the contributory regime of the Colombian Healthcare System among five insurers, called health-promoting companies, which corresponds to approximately 14.6% of the active affiliated population of this regime in the country and 7.3% of the Colombian population. These data were used to calculate the prevalence of motor neuron disease in 2017 in Colombia.

A database designed by the pharmacoepidemiology department of Audifarma S.A., the largest dispenser of medicines in the country, was reviewed and validated by the authors and allowed the collection of variables on drug utilization. Data on outpatients of all ages and genders who had been diagnosed with motor neuron disease according to the International Classification of Diseases (ICD-10) who were prescribed riluzole between April 1 and 30 June 2017 were included.

Sociodemographic variables (gender, age, city) were collected, as well as pharmacological variables (dose of riluzole, quantity dispensed). The defined daily dose (DDD) was used as a unit of measurement for the utilization of this drug and was expressed as DDD per 1,000 patients per day defined inhabitant daily dose (DID). These prescription data can provide a rough estimate of the proportion of the study population treated daily with the drug on average, on any day of the period analyzed.

Comedication was accepted as a surrogate indicator of chronic disease, considering the following circumstances: a) antidiabetics and insulin/diabetes mellitus; b) antiulcer agents/petio ulcer disease; c) psychostimulants/apathy, anhedonia and somnolence; d) antidepressants/depressive

disorder; e) anxiolytics and hypnotics/anxiety or sleep disorders; f) lipid-lowering/dyslipidemia; g) thyroid hormone/hypothyroidism; h) nitrovasodilators/ischemic heart disease; i) antihypertensives and diuretics/hypertension; j) affect stabilizers/bipolar affective disorder; k) antipsychotics/psychosis-schizophrenia; l) anti-dementia drugs/dementia and Alzheimer's disease; m) antithyroid/hyperthyroidism; n) antiepileptic/epilepsy; o) bronchodilators/chronic obstructive pulmonary disease; p) phosphodiesterase/sexual dysfunction inhibitors; q) laxatives/constipation; r) antiemetics/nausea; s) botulinum toxin/spasticity, hyperhidrosis, sialorrhea and urinary dysfunction; t) analgesics or non-steroidal anti-inflammatories/pain; u) other anticholinergics/urinary dysfunction. In such cases, the suitability of riluzole was analyzed based on the pharmacological effects that these medications may have on comorbidity and between themselves.

The total unit costs, the cost of the prescribed average dose and the cost per 1,000 patients/day (cost inhabitant day CID = cost / [365 x No. patients] x 1000) were used to estimate the economic impact of riluzole prescriptions using the reference price of the dispensing company.

For data analysis, the authors used the statistical package SPSS Statistics, version 23.0 (IBM, USA) for Windows. Descriptive statistics such as average, standard deviation and minimum and maximum values were used for continuous variables, and percentages were used for categorical variables.

The protocol received the approval of the Bioethics Committee of the Universidad Tecnológica de Pereira in the category of "research without risk." The bioethical principles established by the Declaration of Helsinki were respected. Personal data of patients was not used and individual informed consent was not required.

RESULTS

A total of 81 patients with motor neuron disease receiving riluzole in the study period were found with an average age of 60.8 ± 12.6 years (range: 29 - 84 years). Distribution by gender showed that 39 were men (48%). According to the age groups, 48 (62%) were younger than 65 years old, 16 (21%) were between 65 and 74 years old and 10 (13%) were 75 or older; no statistically significant differences were found between men and women. The calculated prevalence of motor neuron disease was 2.29 per 100,000 individuals affiliated with the Colombian Healthcare System. The city of Bogotá was home to 35 of the patients (43%), followed by cities such as Cali, Pereira and Armenia, in which no significant differences were found in terms of average age, gender or use of comedication.

Table 1. Comedication in patients with motor neuron disease in Colombia, 2017

Comedication	No. Patients	%
Antidepressants	32	39.5
Other antihypertensives	26	34.5
Antiulcers	20	24.7
Angiotensin II receptor antagonist	18	22.2
Paracetamol	16	19.8
Levothyroxine	13	16.0
Laxatives	10	12.3
Statins	10	12.3
Antidiabetics	8	9.9
Baclofen	6	7.4
Opioids and derivatives	6	7.4
Non-steroidal anti-inflammatories	4	4.9

Source: the authors.

Comedication: Patients with motor neuron disease received riluzole in 50 mg tablets with a mean estimate of 1.07 DDD and 0.016 DDD per 1,000 patients were used per day. Among the patients included in this study, 51 (63%) were concomitantly receiving one or several groups of drugs that reflected comorbidity or may have interacted with riluzole; these are shown in Table 1.

Cost analysis: The total cost of dispensing riluzole during 2017 in the affiliated population was 249,173,604 COP (USD 85,348). The cost of a prescribed daily dose for the 50 mg tablet formulation on average was 6,724 COP (2.3 USD). The CID was 196.2 COP (0.07 USD).

DISCUSSION

This study determined the prescription patterns and estimated the cost of the use of riluzole in a sample of patients with motor neuron disease affiliated with the Healthcare System of Colombia. These findings can be used by health administrators to make decisions aimed at improving health care for patients with this disease. The average age in the population under treatment is lower than that reported in the Europe population at the time of diagnosis (60 vs 65 years) (15), which may be associated with an earlier onset of symptoms in the former; condition according to the results of South American studies with lower averages age than the Europeans (6,16,17).

Regarding distribution by gender, the slightly greater proportion of women (52%) in the analyzed group is striking, as most studies report a ratio of 1.2 to 1.5 men for each woman (15,18-20). This result could be explained

ned, among other things, because women have a greater tendency to consult doctors early in the presence of symptoms and to seek and accept treatment compared to men, which in turn results in underreported conditions among men (21).

The estimated prevalence in the Colombian population is lower than that reported in Antioquia, Colombia (2.3 vs 4.9/100,000 patients). This may be explained because this latter study made an indirect estimation using capture-recapture method (7). The differences in the methodologies used and the results reported are common in most epidemiological studies (22). Similarly, the estimated prevalence in the Colombian population is lower than that reported in European and North American studies (2.3 vs 3.0-6.0/100,000 patients); however, it is consistent with what has been registered in other African American, Hispanic and non-Hispanic populations of European descent, with lower prevalence compared to Europeans (5,15,17-20,23). This figure may be underestimated, given that it is a captive population receiving pharmacological treatment.

Riluzole was used according to the DDD recommended by the World Health Organization (WHO), which reflects the adherence of clinical practice to the recommendations and results in effective clinical trials(24). No studies were found that would allow comparisons of DID in other populations. Although 63% of patients received one or more drugs for the management of symptoms or associated comorbidities, the figure is lower than that observed in a study conducted in Austria among patients with riluzole prescriptions, where the use of at least one additional medication occurred in 97% of the cases (25). The proportion of patients receiving drugs for cardiovascular comorbidities between 12 to 34% is related to that reported in other countries, where this proportion is less than 35% (26,27).

Painful disorders affect a person's quality of life, and in this study, prescriptions for non-opioid analgesics were commonly found, similar to other observations of important uses of acetaminophen and non-steroidal anti-inflammatory drugs(28). This is probably due to the precaution regarding the risk of ventilatory failure with the use of opioids, despite the fact that six patients were identified who received them. The prescription of antidepressants in the study group (39.5%) is higher than the reported prevalence of depression in patients with ALS; that is, between 24 and 28%. This is related to the impact generated at the time of diagnosis of a neurodegenerative disease, which is widely described (27). On the other hand, it is possible that the use of this group of drugs is high if its usefulness as a coadjuvant in pain management is considered. The use of laxatives in this study was lower (12%) than that reported in other patients with motor neuron disease worldwide (21

to 46%), a difference that could be related to an increased use of drugs that cause constipation in the latter, such as calcium-antagonists, opioids, antipsychotics and calcium supplements (25,26) or that this symptom is not being managed pharmacologically in the former.

The presence of cramps in patients with motor neuron disease is frequent and varies among populations (28). In a survey conducted in North America, 97% of patients reported having cramps at some time (29), so the infrequent prescription of muscle relaxants is surprising. This could reflect that cramps (despite being frequent) do not significantly alter the functionality of the patient or that this symptom is not being treated by physicians. One study suggests a correlation between the use of centrally acting muscle relaxants (baclofen) and improved survival rates of patients with ALS (25); however, extensive investigations are necessary to determine this possible benefit. The dispensing of proton pump inhibitors was relatively low compared to other pharmacological groups. A study by Cetin et al. (25) found that the use of these medications could have a negative impact on the survival of patients with motor neuron disease; however, more studies are required to validate these results. Some studies suggest that the use of statins may have a negative role in the survival of patients with ALS (30,31), although only 12% of patients received this group of drugs. Thus, this relationship is not clearly demonstrated, and their use is still controversial (30-32). Finally, the significant percentage of patients taking thyroid hormones (16%) is interesting. Various investigations have failed to associate thyroid disease or thyrotropin levels (TSH) with ALS or its evolution (33,34).

It is likely that riluzole's prescription pattern is uniform among Colombian cities included in the study regarding adherence by the medical staff to dosage recommendations based on clinical trials of the drug (24). Variability in medical care is not a usual finding in pharmacoepidemiological studies, particularly in the prescription habits of medications (22). However, it should be considered that the number of patients is limited.

Regarding the economic impact, although there are no studies evaluating the units of measurement of direct costs of riluzole used in the present study to allow accurate comparisons, it was established that the total and annual costs per patient were three to ten times lower than that reported in the United States, Canada, Spain and the United Kingdom (12,13,35-38). Other relevant expenses were not considered, such as hospitalizations due to complications related to the illness, medical consultations by specialists or indirect costs.

This research has limitations related to the nature of observational studies, the interpretation of certain findings and the generalization of the results, as the information was obtained from databases and not directly from patients or

prescribers. Medical records were not consulted, which will be addressed in additional studies in the second phase of this line of research that includes clinical data such as disease phenotype based on electrophysiological criteria, adherence to treatment, incidence of adverse reactions attributable to medication, complications, results of diagnostic tests and the effects of other therapeutic interventions, such as the use of positive pressure devices, alternate feeding routes and nutritional interventions, among others. Although this analysis was carried out with all the patients identified with ALS in the target population, its findings cannot be extrapolated to the entire country.

CONCLUSIONS

From the above findings, it can be concluded that the use of riluzole in patients with motor neuron disease in Colombia is carried out at the doses recommended by the WHO based on clinical trials in subjects with an average age of 61 years who are affected by other comorbidities and conditions, such as depression, hypertension, pain

and hypothyroidism. These comorbidities are relevant to identify drugs that can interact and modify the therapeutic response at a direct cost lower than that reported by other countries. Further studies are recommended to determine the effectiveness of riluzole in real-life conditions.

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Ethical publication statement

The authors confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with this guideline.

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