ORIGINAL RESEARCH

Predictors Of Marketing Authorization Status Of Dipyrone Within A Country

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Abstract

Introduction. Although there are numerous data about increased risk of bone marrow toxicity with dipyrone when compared to other nonsteroid anti-inflammatory drugs, it continues to be marketed in many countries. The aim of this study was to identify currently unknown putative predictors of dipyrone having marketing authorization in a country.

Methods. The study was designed as secondary research of a cross-sectional type. The data were collected from web pages of relevant international and national entities. The main outcome variable of the study was dipyrone marketing authorization status within a country. The data were analyzed by both uni- and multi-variate statistics, including logistic regression.

Results. The following factors showed significant influence on marketing authorization status of dipyrone: Current Health Expenditure per capita ($p = 0.02$), Gross Domestic Product per capita ($p = 0.02$), Incarceration Rate (per 100.000 population) ($p = 0.04$), and overall Global Innovation Index ($p = 0.04$). However, after adjustment, the multivariate analysis showed that the most important predictor was Current Health Expenditure per capita ($p = 0.01$).

Conclusion. The use of medications already considered by many to be obsolete and even dangerous due to their low benefits/harm ratio seems related to the underdevelopment of a country. There is a need for further research into ways to help these countries make better choices about the use of potentially harmful drugs and other health technologies.

Keywords: dipyrone, bone marrow toxicity, marketing authorization, predictors.

INTRODUCTION

Dipyrone, or metamizole, is a well-known analgesic, anti-inflammatory, antipyretic and spasmolytic medication (1) released in the drug market in 1922 (2), belonging to class of nonsteroid anti-inflammatory drugs (NSAIDs). However, it is surrounded by controversy when it comes to safety issues (3). It has been prohibited in various countries, such as the United States of America and the United Kingdom (2), for its potential life-threatening damage to the bone marrow. It may cause agranulocytosis (3), which consists in a neutrophil count of less than 500 cells per microliter of blood (2). A report from EudraVigilance pharmacoviligance database, using data mostly from Germany and Switzerland

between 1985 and 2017, registered 1,478 cases of agranulocytosis in the reporting period, marking forty-three percent of those as life-threatening and sixteen percent as fatal. Nonetheless, the authors also state the difficulty in getting a true incident rate for this event since it is underreported and there are a lot of opposing data reported by different countries, like Germany, that estimates a rate of 7.9 cases per million prescriptions, and Sweden stating 1 case per 1,400 outpatients based on ten spontaneous reports and data from drug sales (2).

The marketing ban on this medication is mostly due to the aforementioned controversial occurrence of agranulocytosis that may come with its use (4). However, in contradiction to those that have banned this drug for decades now, there are many countries that still rely on metamizole daily. As a result, dipyrone is still largely produced and utilized in many Central and South American, European, Asian and African countries (5). It is also illegally sold due to higher efficacy when compared to other NSAIDs (5), being referred to as the "Mexican aspirin" (6) and commonly used by families whose countries of origin still allow it (5), creating sometimes a family pattern of agranulocytosis (6). There are certain authors who associate its marketing clearance with the nations classified by some as the "Third World" (7).

Although occasionally mentioned, social-economic variables are still understudied as a contributing factor to this drug's marketing clearance. A study conducted in San Diego, California, stated that dipyrone use in low-income Hispanic people is a problem, but added that the use of the medication, and its possible fatal side-effects, may not be limited to low-income people and even warrants the need for a social-economic overview of the matter (6). Against this backdrop, and given that many developed nations still allow it, the aim of our research was to identify currently unknown putative predictors of dipyrone having marketing authorization in a country.

METHODS

Patients and study design

The study was designed as secondary research of a cross-sectional type. The data were collected from web pages of World Health Organization (Global Health Expenditure Database) (8), United Nations (9), Trading Economics (10), International Monetary Fund (11,12), the World Population Review (13,14), UNESCO database (15), Global Report of Human Development Index (16) and Global Innovation Index Report (17). Certain variables that could not be found at the web pages of these entities were searched for in publications from medical journals, using the MEDLINE database.

Methods

The data were searched for and extracted from the above-mentioned web pages by a junior author, and the senior author checked the quality of the search and extraction. The literature search and data extraction were conducted from July 2, 2024 to July 11, 2024.

The population of the study were countries as political entities. The sample of the countries was taken as a convenience sample, i.e., the countries with all necessary accessible data were selected. The sample size was calculated based on binary logistic regression, where the outcome was whether dipyrone is allowed for use or not by a country's health authorities. With power of the study being 80%, probability of statistical error type one being 0.05, expected odds ratio of 0.05, expected R2 value of 0.1 and assuming normal distribution, minimum sample size was 23 countries. The calculation of the sample size was made by G*power software, version 3.1.9.7.(18).

The main outcome variable of this study was dipyrone status within a country (whether having marketing authorization or not), and putative predictors were: Cu-

rrent Health Expenditure (CHE) as % Gross Domestic Product (GDP), Current Health Expenditure (CHE) per capita in US$, Gross Domestic Product (GDP) per capita in US$, population (in thousands) (8), unemployment rate (10), General Country Gross Debt (% of GDP) (11), inflation rate, average consumer prices (annual percent change) (12), completion rate, upper secondary education, both sexes (%) (15), Human Development Index (HDI – composite index calculated from data on life expectancy, education (length of schooling), and per capita income) (16), Crime Index (per 100.000) (13), Incarceration rate (per 100.000 population) (14), Overall Global Innovation Index (the average of a country's innovation input and output, with 81 parameters involved in calculation) (17), developed/developing status according to the UN classification of nations (9) and continent where a country is situated.

Statistical analysis

The extracted data were first tabulated and checked for errors or inconsistencies. The values of continuous variables were described according to the groups defined by dipyrone status using measures of central tendency (mean and median) and variability (standard deviation and interquartile range), and values of categorical variables by frequences and percentages. Normality of data distribution was checked by the Kolmogorov-Smirnov test. The differences among the study groups were tested for statistical significance by the Mann-Whitney U test (for continuous variables) or by Chi square of the Fischer exact test (categorical variables). Multivariate data analysis was made by binary logistic regression, using forward addition method for building the regression model. Validity of the model was checked by the Hosmer-Lemeshow test and explaining potential of the model by Cox and Snellen and Nagelkerke R2. The results of the analysis were shown by odds ratio and 95% confidence intervals.

RESULTS

The total of 23 countries were included with complete data available over the Internet; thirteen countries – the Russian Federation, Mexico, Brazil, Israel (19), Egypt, Serbia (20), South Africa (21), New Zealand (22), China (23), Austria, Portugal, (24), Argentina (25) and Spain (26) – still allow the use of dipyrone, which currently possesses marketing authorization. Meanwhile, ten countries – Sweden, USA, Japan, Iran, Australia (19), UK, France, Canada (23), Nigeria (27) and Ireland (28) – banned its use and/or withdrew marketing authorizations granted in the past. Values of various indicators of socioeconomic status or investment in healthcare per country according to whether dipyrone is allowed for use or not are shown in Table 1.

When multivariate analysis of variables associated with dipyrone status in a country (allowed or not allowed) was made using binary logistic regression, the acceptable model included only two variables, Current Health Expenditure (CHE) per Capita in US$ and Human Development Index (Hosmer-Lemeshow test Chi Square = 9,725, dr = 8, p = 0.285; Cox & Snell R Square = 0.469, Nagelkerke R Square = 0.629). Only CHE per capita was significantly associated with dipyrone being allowed for use, but in reverse, acting as a protective factor: Odds Ratio (OR) = 0.998 (95% Confidence Interval = 0.0015), p = 0.01.

DISCUSSION

After univariate analysis of our data, the following factors showed significant influence on marketing authorization status of dipyrone: Current Health Expenditure (CHE) per capita in US dollars, Gross Domestic Product (GDP) per capita in US dollars, Incarcerated Rate (per 100.000 population) and overall Global Innovation Index (GII). However, after adjustment, the multivariate analysis showed that the most important predictor was Current Health Expenditure (CHE) per capita in US dollars.

Table 1. Values of the study variables according to status of dipyrone (expressed as mean ± standard deviation, median [interquartile range]) in the study sample of countries.

Variable		Dipyrone allowed (n = 13)	Dipyrone not allowed (n = 10)	Statistical significance of difference (p)
Current Health Expenditure (CHE) as % of Gross Domestic Product (GDP)		7.63 ± 1.93, 8.62 [3.59]	9.25 ± 3.39, 9.48 [3.59]	0.10
Current Health Expenditure (CHE) per capita in US$		1464.32 ± 1401.85, 712.28 [2730.74]	3899.8 ± 2486.96, 4318.49 [2730.74]	0.02
Gross Domestic Product (GDP) per capita in US$		17,141.28 ± 14,211.67, 9,756.13 [29,545.14]	37,327 ± 20,249.34, 42,291.6 [20,545.14]	0.02
Population (in thousands)		160,570.64 ± 365,563.96, 45,518.3 [119,565.42]	97,583.98 ± 96,156.26, 64,967.7 [119,565.42]	0.69
Unemployment rate		0.08 ± 0.07, 0.06 [0.02]	0.05 ± 0.01, 0.04 [0.02]	0.48
General Country Gross Debt (% of GDP)		0.73 ± 0.24, 0.75 [0.73]	0.95 ± 0.69, 1.04 [0.73]	0.78
Inflation rate, average consumer prices (annual percent change)		0.24 ± 0.68, 0.04 [0.12]	0.09 ± 0.13, 0.02 [0.12]	0.28
Completion rate, upper secondary education, both sexes (%)		0.76 ± 0.09, 0.76 [0.34]	0.8 ± 0.17, 0.88 [0.34]	0.23
Human Development Index (HDI)		0.83 ± 0.07, 0.82 [0.09]	0.87 ± 0.13, 0.92 [0.09]	0.07
Crime Index (per 100.000)		47.62 ± 15.31, 47 [18]	43,07 ± 17.94, 46.9 [18]	0.87
Incarcerated rate (per 100.000 population)		191.46 ± 88.25, 173 [131]	156.81 ± 152.81, 109 [131]	0.04
Overall Global Innovation Index		43 ± 23.23, 49 [36]	29.22 ± 34.71, 15 [36]	0.04
UN classification of nations	Developing	6 (46,2%)	2 (20%)	0.379
	Developed	7 (53,8%)	8 (80%)	
Continent	Europe	5 (38,5%)	4 (40%)	0.963
	North America	1 (7.7%)	2 (20%)	
	Asia	1 (7.7%)	1 (10%)	
	Middle East	1 (7.7%)	1 (10%)	
	Africa	2 (15,4%)	1 (10%)	
	Oceania	1 (7.7%)	1 (10%)	
	South America	2 (15,4%)	0 (0%)	

Individually speaking, the CHE in USD reflects the amount spent on healthcare per person in each population, using the American currency as a unit of measurement, and aiming to enable a comparison between nations (29). This has been shown to be a protective factor, therefore, the higher its value, the less likely it is that a country will still allow dipyrone to be marketed. A higher value of this variable indicates more considerable investment in the health system. Consequently, it is possible to infer that there is a more developed medical infrastructure in the country, not only in the clinical aspect, but also in pharmacovigilance and in the sectors responsible for authorizing the sale of medications. In this way, there is a better assessment of the balance between risk and benefit of a drug, as in the case of metamizole. A Chinese study similarly associated fiscal spending on health and the pharmaceutical industry's stock index, concluding that by controlling the former it is possible to achieve sustainable management of the latter, characterizing a directly proportional relationship between them (30).

The variable GDP demonstrates the wealth of population in a given country in US dollars, and is comparable internationally (31). It is an indicator that acts in a very similar way to the CHE on the marketing authorization status of dipyrone. It also plays a protective role and is associated with the existence of drug regulatory agencies with greater funding and more rigorous process of granting marketing authorization. An African study showed that for an effective pharmacovigilance system to ensure the

safety and control of medications, adequate funds are also necessary, or this function cannot be guaranteed (32).

Regarding the Incarceration Rate, it consists of the number of people arrested in proportion to its total population, being measured per 100,000 inhabitants and illustrating part of the criminal reality of a country due to the influence it suffers from the number of crimes, the policing and prosecution rates, time served in prison, etc. (33). In this case, it was found to be a risk factor for the marketing authorization of metamizole as it could reflect economic and social problems that also affect the health sector and the quality of its services. The literature pointed out that the effects of mass incarceration in the health area affect not only the families of those arrested, but the community and the country as a whole (34).

The GII uses around 80 indicators from different areas, from political and environmental, to technological and educational, to try to rank the most innovative economies in the world and monitor their position and progress or regression, comparing them internationally (35). In this way, it also behaved as a protective factor against the marketing authorization of dipyrone as it represented greater access and incentive to technology, medical advances and, consequently, more modern and regulatory pharmacovigilance. Similarly, a Brazilian study that correlated the health system with innovations in the pharmaceutical industry declared a favorable repercussion derived from this relationship (36).

Furthermore, the Human Development Index (HDI) is based on data from three major areas: health, education and economy. To assess health, life expectancy at birth is used. For education, the average years of study for adults and expected years of study for children are analyzed. Finally, the economy is illustrated by gross national income per capita. The final number after logarithmic transformation varies between 0 and 1, with 1 being the best possible value (37). Countries with a higher HDI are more likely to have better health and pharmacovigilance systems and a population with higher level of knowledge, contributing to the prohibition of metamizole and acting as a protective factor. Although in our study its influence did not reach statistical significance, there was a clear tendency.

When it comes to study limitations, there are two factors to be considered: small sample size and choice of variables. The first was due to unavailability of information about the study variables for many countries, which is why important predictors may have been lost in the process due to the small statistical power of the study. The second factor is present because information on some potentially important variables was not publicly available, e.g., the political stability of a country, etc.

CONCLUSION

The use of medications already considered by many to be obsolete and even dangerous due to their low benefits/harm ratio seems related to the underdevelopment of a country, not only in an economic context, but also in educational, cultural, scientific and social contexts in general. There is a need for more research into ways to help these countries make better choices about the use of potentially harmful drugs and other health technologies.

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Authors' Contributions: Slobodan Janković devised the main idea of the study, designed the study plan and protocol, performed statistical analysis and wrote the paper. Isabella de Avellar Ramos participated in the study design, searched the literature, collected the study data and tabulated it, participated in the statistical analysis and wrote the paper.

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