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Analysis of adrenaline autoinjectors acquisition in Portugal over 15 years

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Key words

Adrenaline autoinjector; anaphylaxis; acquisition; prescription; prevalence.

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Impact statement

The acquisition of adrenaline injectors could be a predictor in the prevalence of patients at risk of anaphylaxis.

Summary

Background. *The adrenaline autoinjector (AAi) is universally recommended as the first-line treatment for anaphylactic reactions occurring outside the medical setting. The quantification of its acquisition may help estimate the prevalence of patients at risk of anaphylaxis with an indication for AAi.* ***Aims.*** *Evaluation of the global and regional frequency of AAi purchases in Mainland Portugal between 2003-2017 and calculate the inherent costs in 2017.* ***Methods.*** *AAi acquisition distribution analysis along this period. The population was divided in two age groups according to the adrenaline dosage.* ***Results.*** *A total of 10,993 AAi units of 0.15 mg/0.3 mL and 28,619 of 0.3 mg/0.3 mL were acquired in these 15 years, with an annual average of 733 and 1908 units, respectively. In cumulative values terms, Lisbon showed the highest number of AAI acquired and higher prevalence per region/100,000 inhabitants in both groups. In 2017, the annual cost for each age group was €64,202.71/€187,447.70 for patients and €37,706.35/€110,113.30 for the National Health System.* ***Conclusions.*** *In the last 15 years, there was a progressive increase in AAi acquisition. We estimate a rate of anaphylaxis occurrence in Portugal according to AAi acquisition of 0.165%.*

Introduction

Anaphylaxis, according to the World Allergy Organization (WAO), is defined as a potentially fatal severe systemic hypersensitivity reaction of sudden onset after exposure to an allergen (1, 2). Since it is a medical emergency, early treatment is critical. Intramuscular adrenaline is the first-line treatment for this emergency, and its dosage should be adjusted according to the patient weight (3, 4). Given that most episodes of anaphylaxis occur in the community, *i.e.*, outside the medical setting, the adrenaline autoinjector (AAi) should be prescribed to patients at risk of anaphylaxis recurrence (5, 6).

The European Academy of Allergy and Clinical Immunology (EAACI) in 2014 published the guidelines on anaphylaxis, which includes indications for the prescription of this device (7).

Existing data on the prevalence and incidence of anaphylaxis are inaccurate and correspond to default estimates since this pathology is often underdiagnosed or underreported. Based on publications between 2010 and 2015, the estimated frequency of anaphylaxis is 50-112 episodes per 100,000 inhabitants-year, estimated prevalence of 0.3% to 5.1% (8-12).

In Europe, 2 to 8 cases per 100,000 inhabitants/year have been estimated, with a growing trend, inferring that approximately 0.3% of the European population is at risk of having an episode of anaphylaxis at some point in their life (13). Some population-based studies estimated a rate of occurrence of anaphylaxis based on the acquisition of AAi ranging from 0.083% (10) to 0.95% (9), corresponding to the acquisition of 83 units of AAi and 954 units per 100,000 inhabitants in Israel and Canada, respectively.

In Portugal, based on the notified cases of anaphylaxis in the Catálogo Português de Alergias e Outras Reações Adversas (CPARA), Amaral *et al.* (14) recorded 1209 cases of anaphylaxis during a period of 10 months in a total of 20,389 records, corresponding to 6% of all adverse reactions reported in this catalogue. The most frequent groups of allergens inducing anaphylaxis reactions were drugs (83%), foods (7%) and Hymenoptera venom (3%). Of these allergens, the AAi is only indicated for food and venom allergy, corresponding in this study to a prevalence of patients with indications to AAi of 1.12/100,000 inhabitants (14).

The prevalence of patients at risk of anaphylaxis based on AAi acquisition and the annual cost inherent to these devices acquisition in Portugal are unknown. Our aim was to evaluate the frequency of AAi acquisition in Mainland Portugal during a period of 15 years (2003-2017), and to calculate the economic impact in terms of cost inherent in its acquisition for the patients and the National Health System (NHS). We also estimate the risk of anaphylaxis occurrence based on this data.

Materials and methods

The frequency distribution of AAi acquisition in Portugal between 2003 and 2017 was analyzed through data provided by INFARMED (National Authority of Medicine and Health Products I.P.). During this period, two brands of AAi were marketed with 0.15 mg/0.3 mL and 0.3 mg/0.3 mL dosages.

To adjust the dosage to weight and age, the studied population was divided into two age groups: group A – patients aged between 5 and 9 years for the 0.15mg dose, and group B – patients older than 10 years (≥ 10) for the 0.3 mg dose.

The doses relating to bodyweight recommendations are based on limited pharmacokinetic data in healthy volunteers. No pharmacokinetic or pharmacodynamics studies involving patients with anaphylaxis have been published. They are also based on consensus and standard practice. For children under 15 kg adrenaline autoinjectors are not usually recommended; the recommendation for children 15-30 kg is a 0.15 mg adrenaline autoinjector device and for children over 30 kg and adults an 0.3 mg adrenaline autoinjector device (2, 15). Considering that, according to the growth reference values of Portuguese children, a 5 years old child has an ideal weight of 18.4 kg and a 10 year old child 31.9 kg, we chose to use the range of 5-9 years and over 10 to define the age groups.

The prevalence/inhabitant calculation was performed using the National Statistics Institute database for Mainland Portugal resident population during this period, based on the 2011 census. The devices acquisition per geographic regions (North, Center, Lisbon, Alentejo and Algarve) according to the Nomenclature of Territorial Units for Statistical (NUTS 2013) was also calculated. Considering the price of the devices in 2017, the inherent cost to the patient and the NHS was evaluated.

Data analysis was performed using Microsoft® Excel 2016. Data were anonymized and patient confidentiality was guaranteed. The study protocol was approved by the Ethical Board of Centro Hospitalar Universitário de Lisboa Norte.

Results

We show in **figure 1** the distribution of the frequency of AAi acquisition.

In 2003 and 2017, the lowest and highest numbers of AAi units were acquired for both doses, respectively. There was a progressive increase in acquisition over the years for both dosages. For the 0.15 mg dose, there was with an average increase of 117 units per year, with the largest increase from 2010 to 2011, representing an increase of 389 units acquired. The average annual increase for 0.3 mg dose was 349 units per year with the most significant increase occurring from 2016 to 2017, representing an increase of 1368 units acquired (**figure 1A**).

The prevalence of acquisition per inhabitant in 2003 for the dose of 0.15 mg was 13 per 100,000 inhabitants, followed by a progressive increase in AAi dispensed, reaching a maximum of 376 per 100,000 inhabitants in 2017, which correspond to a total average of 144 units per 100,000 inhabitants acquired over these 15 years. For the 0.3 mg dose, in 2003 the prevalence was also the lowest, with a total of 3 units acquired per 100,000 inhabitants, and in 2017 the largest (58 per 100,000 inhabitants), corresponding to a total average of 21 units per 100,000 inhabitants acquired for the 0.3 mg formulation (**figure 1B**).

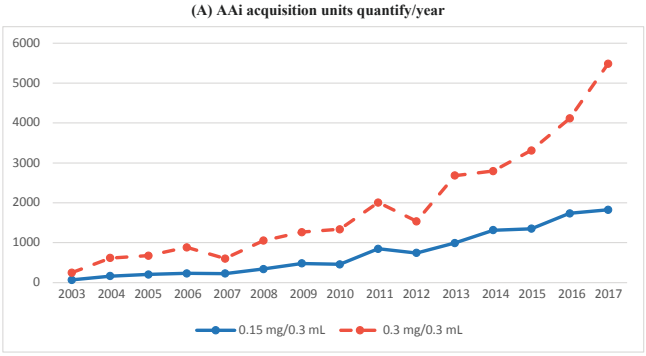
According to our data, based on the adrenaline acquisition over these 15 years, it is possible to predict a population-at-risk of anaphylaxis ratio of 0.165%. This corresponds to a dispensing average of 165 units of AAi per 100,000 inhabitants.

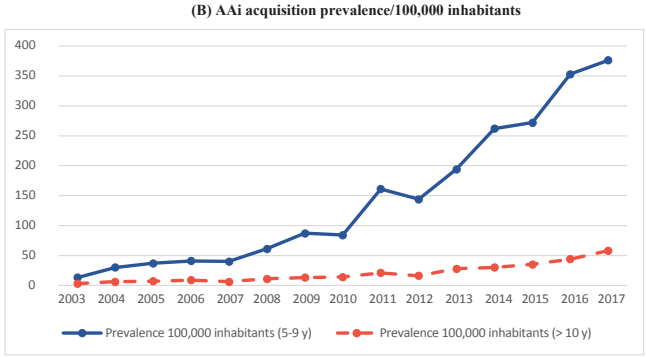
Regarding the cumulative value of devices purchased per year and region, Lisbon was the one with the most AAi devices purchased in both marketed doses: A: 40%, B: 43%, followed by the North with A: 32%, B: 25%, the Center region with A: 21%, B: 23%, Algarve with A: 4%, B: 5% and Alentejo with A: 3%, B: 4% (**figure 2**).

In the last year of the study, in terms of acquisition prevalence per 100,000 inhabitants in the different regions, Lisbon continued to be the one with the most units dispensed (84), followed by the Center region – 75, Algarve – 73, North – 71 and finally Alentejo – 33 (**table I**).

Also, in 2017, considering the two brands marketed in Portugal, the average cost per device has A: €55.81 and B: €54.29. With the NHS co-payment of 37% since 2009, cost per unit per user (A/B) was €35.16/€34.20 and for the NHS €20.65/€20.09, which corresponds to an annual cost of €64,202.71/€187,447.70 for users and €37,706.35/€110,1103.30 for the NHS. These data are summarized in **table II**.

Figure 1 *- Adrenaline autoinjector acquisition in Mainland Portugal 2003-2017.*

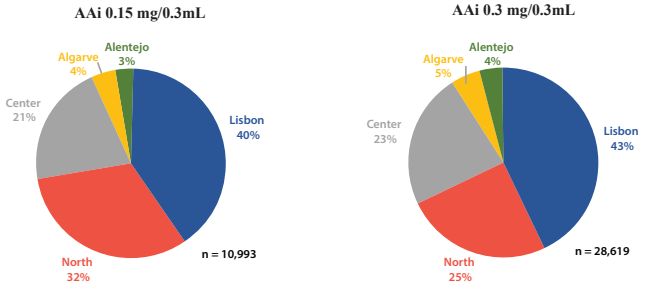




Population A (5-9 years): 544,632 on 2003; 546,190 on 2004; 552,868 on 2005; 557,881 on 2006; 559,471 on 2007; 559,132 on 2008; 553,680 on 2009; 540,608 on 2010; 527,769 on 2011; 518,699 on 2012; 510,652 on 2013; 503,601 on 2014; 497,237 on 2015; 292,355 on 2016; 486,308 on 2017.

Population B (> 10 years): 9,350,364 on 2003; 9,375,678 on 2004; 9,376,306 on 2005; 9,417,926 on 2006; 9,446,232 on 2007; 9,471,501 on 2008; 9,496,226 on 2009; 9,526,009 on 2010; 9,535,039 on 2011; 9,510,688 on 2012; 9,474,419 on 2013; 9,440,820 on 2014; 9,417,757 on 2015; 9,460,792 on 2016; 9,387,089 on 2017. *Data from the National Statists Institute.

Figure 2 *- Adrenaline auto-injector acquisition distribution per geographic regions 2003-2017.*



Discussion

According to our results, in the last 15 years there was a large increase in AAi acquisition by 26 times for the pediatric patients and by 21 times for adolescents/adults. Other published studies also showed an increase, although of a lower magnitude. For example, Levy *et al.* (10) demonstrated an increase in AAi acquisition by the population of Israel between 1997 and 2004 of 59% in the pediatric formulation and 89% in that of adolescents and adults. The review of pharmaceutical data in Australia between 1998 and 2002 by Kemp (16), demonstrated an increase in AAi dispensing to pharmacies by 300% of the pediatric formulation and 193% of the adolescents and adult's formulation. In the United Kingdom, the increase in AAi prescription over 13 years (1991-2004) was 1200% (17).

The increase can be explained by the higher reports on food and venom anaphylaxis cases but also by the NHS co-payment that has been in existence since 2009, acquisition by the health professionals themselves such as private clinics, dentists and immunoallergologists, and better knowledge through health education training within medical professionals, and due to the short expiration date of the device.

There was a higher AAi acquisition rate per inhabitant in the younger group in relation to the adolescent/adult group, which is in accordance with other studies published (9-11, 18-20).

Simons *et al.* (9), using a pharmaceutical database, analyzed data from all formulations of epinephrine dispensed for 5 years in Manitoba (Canada), demonstrating an average dispensing rate of 1.44% in patients under 17 years and 1.22% in patients over 17 years of age. Taking into account the age distribution used to account for the AAi dosage and the number of people included in each group, over the 15 years, our study predicts an average dispensing ratio per 100,000 inhabitants of 0.144% for the 5 to 9 years group, and 0.021% for the group aged 10 years or more, comparatively much lower for both groups.

According to our data it is possible to predict a population-at-risk of recurrent anaphylaxis ratio of 0.165%. This corresponds to a dispensing average of 165 units of AAi per 100,000 inhabitants. This value is in the range of other studies published using the same methods (9,10). Levy *et al.* predicted an incidence of anaphylaxis of 0.083% (83 per 100,000) in the Israel population between 1997-2004 (10). The other study estimated the occurring anaphylaxis rate in the population of Manitoba, Canada (1995-2000) at 0.95% (954 per 100,000) (9). Our frequency is within the limits published on other studies but lower than this last study, allowing us to infer that in Portugal, as in many other countries, anaphylaxis is underdiagnosed and underreported. Besides that, anaphylaxis seems to be undertreated; even if it is properly diagnosed, some patients are not prescribed with AAi – *e.g.*, in the emergency department –, and even if it is prescribed,

Table I *- Adrenaline autoinjector acquisition distribution per geographic regions in 2017.*

Geographic Region	AAi 0.15 mg/0.3 ml*	AAi 0.3 mg/0.3 ml*	Mean population years/ region 2017**	Prevalence/region (A+B) 100,000 inhabitant 2017**
Alentejo	34	203	715,019	33
Algarve	65	261	440,543	73
Center	399	1309	2,237,640	75
Lisbon	738	2206	3,580,390	84
North	590	1452	2,827,514	71
Total	**1826**	**5481**	**9,801,106**	**336**

AAi: adrenaline autoinjector; *data from the National Health System (NHS)/National Authority of Medicine and Health Products I.P. (Infarmed); **data from the National Statistics Institute.

Table II *- Adrenaline auto-injector costs in 2017.*

Parameters	Adrenaline auto-injector dose	
	0.15 mg/0.3 mL	0.3 mg/0.3 mL
Average price/unit (€)	55.81	54.24
NHS co-payment (37%)/unit (€)	20.65	20.09
Cost per patient (€)	35.16	34.20
Cost for patients in 2017 (€)	64,202.71	187,447.70
Cost for NHS in 2017 (€)	37,706.35	110,113.30

NHS: National Health System.

they often do not acquire it, mostly because of the price or because they don't understand when or how to use it.

Regarding the distribution per geographic region, Lisbon contributed the highest percentage of devices purchased for both dosages, either in terms of the cumulative average value of devices purchased per year per region or per 100,000 inhabitants, while Alentejo consumed the least, substantiating that the consumption is proportional to the population density.

In our study, in both groups, there was a progressive increase in the prevalence of AAi acquisition, which also denotes an increase in the prevalence of patients at risk of anaphylaxis, reaching in 2017 a consumption of 434 units per 100,000 inhabitants that represents a 0.43% rate of population at risk of anaphylaxis in our country this year, closer to world values (21, 22).

Considering that this is an analysis of acquisition, this study showed a higher number of anaphylaxis cases per 100,000 inhabitants compared to another Portuguese study (14), which evaluates the registry of anaphylaxis cases in the CPARA (which only represents anaphylaxis reports done by an healthcare professional), implying that could have a underreport by health professionals, since a large number of cases in the CPARA correspond to drug allergy, in which case AAi prescription is not indicated. However, our data is not a direct estimate of the number of anaphylaxis cases. We use a "surrogate marker" of anaphylaxis cases to estimate the frequency of its occurrence. The crude (not per patient) AAi acquisition data may have 2 or 3 devices per year for the same anaphylaxis patient; that is a major difference between our data and CPARA.

Patients with a previous history of anaphylaxis should be studied in an Immunoallergology outpatient clinic to obtain a correct diagnosis and adequate therapeutic orientation in order to reduce the risk of future reactions. Although the guidelines promote the AAi device prescription (7), as well as referral to specialized consultation, this is often not verified. Some studies have shown that the percentage of patients observed in the emergency department with suspected anaphylaxis for whom AAi is prescribed varies between 16-63% (23-25) and that the percentage of referral to a specialized consultation ranged from 11-33% (26-28). Some factors that may contribute to these low rates are the high cost of the devices, waiting lists for the specialized consultation conditioning delays in the study or withdrawal by the patients themselves, and also the non-acquisition of AAi due to the expiration of the prescription.

In 2017 the AAi acquirement in Mainland Portugal reached the maximum of units acquired implying increased costs. The annual cost for the 0.15 mg AAi dose corresponds to about

€65,000.00 for pediatric patients, and for the NHS about €38,000.00 with an average cost per device of €35.16. Diwakar *et al*. in 2017 reported that the UK's current annual expenditure on AAi for children is approximately £7,000,000.00 with an average cost per unit of £25.80 (29).

For the adolescent and adult population, the annual cost in 2017 was about €190,000.00 for the patient and €111,000.00 for the NHS, with a cost per device of €34.20. Patel *et al*. (30) estimated that the AAi device acquisition correspond to an annual average cost of $20 million for devices purchased (cost/device $51).

The frequency of population-at-risk of anaphylaxis and its treatment, namely the acquisition of AAi, impose high costs. Despite the current 37% co-payment by the NHS for these devices, the cost is still high since annual renewal is necessary. Compared to the UK, an AAi is less expensive in the countries where the medium monthly income is higher.

Some limitations of our study are that although is divided per age groups, age range < 5 years is not included since the adrenaline dose must be adjusted for weight and at these ages is rarely prescribed. The etiology of anaphylaxis for which AAi was prescribed is not known, as the main cause of adult anaphylaxis is drug allergy, and in this case AAi device is not indicated. Also, the fact that is an acquisition and not a prescription study and the acquisition depend on the patients. Population division in urban and rural areas was not possible, which would be important due to the higher prevalence of anaphylaxis to Hymenoptera in rural areas. However, there was a higher rate of anaphylaxis in areas with higher population density as expected.

There has also been a greater education for health among professionals in the most diverse areas. This also allows a greater number to be aware of the need for prescribing adrenaline in some patients. Children are very common to carry more than one device, even if it is not mentioned in the guidelines (*e.g*., one at home, one at school, one at grandparents' home), this may leads to an overestimation of the prevalence of patients at risk using this methodology. We estimate the rate of patients at risk for anaphylaxis is based on acquired AAi but not the total anaphylaxis rate in Mainland Portugal.

Conclusions

In the last 15 years, there has been an increase in AAi acquisition for both the pediatric age and adolescents/adults. The significant rise in the number of prescriptions per year suggests an increase in the prevalence of patients at risk of anaphylaxis based on acquired AAi in Mainland Portugal reaching 0.165%.

The authors also justify the significant increase in AAi acquisition, not only due to the rise in anaphylaxis cases frequency, but also as a result of the greater knowledge through health education training in the population and medical professionals, as well as the AAi device co-payment by the NHS in recent year.

Fundings

None.

Conflict of interests

The authors declare that they have no conflict of interests.

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