



ORIGINAL RESEARCH

Trends in adrenaline (EpiPen) dispensing in Israel in 1997–2004

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KEYWORDS

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Summary *Background:* The prevalence of allergic diseases has increased over the last 20 years in the Western world. Reports on the growing use of adrenaline auto-injectors (EpiPen and EpiPen Jr) in several countries may point to increased rates of anaphylactic reactions, increased awareness of the risk of anaphylaxis or both. *Objectives:* To evaluate the dispensing rate of EpiPen units in Israel from 1997 to 2004.

Methods: The database of the General Health Services (Clalit) was searched to determine the number of EpiPen units dispensed each year from 1997 to 2004. Data on mortality from anaphylaxis were derived from the Central Bureau of Statistics using International Classification of Diseases, 10th revision codes.

Results: The dispensing rate of EpiPen units rose gradually from 1689 in 1997 to 2981 in 2004; an overall increase of 76%. No case of death from anaphylaxis was reported from 1998 to 2000.

Conclusions: The dispensing rate of adrenaline auto-injectors has increased considerably over the last 8 years in Israel, although to a lesser degree than in other countries. This is probably a reflection of updated medical policies, in accordance with the clinical guidelines for the management of anaphylaxis and improved public education. Further studies are needed to determine the prevalence of anaphylactic reactions in Israel.

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Introduction

Atopic diseases are an important source of patient morbidity and healthcare utilization. A recent study from the UK showed that 39% of children and 30% of adults have been diagnosed with one or

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more atopic conditions (allergic rhinitis, anaphylaxis, asthma, conjunctivitis, eczema/dermatitis, food allergy and urticaria/angioedema), and that allergic diseases account for 6% of all general practice consultations and 0.8% of all hospital admissions.¹

Anaphylaxis is a severe, rapidly progressive and potentially life-threatening allergic reaction. Potential triggers include foods, insect venom, latex rubber, medications and vaccines.² It occurs more commonly in the community than in healthcare settings.³

Adrenaline injection is the treatment of choice. Fatalities during anaphylaxis are usually due to delayed administration of adrenaline and to severe respiratory complications, cardiovascular complications or both.³ The standard of management for patients with a history of anaphylaxis is prescription of self-injectable adrenaline (EpiPen, EpiPen Jr) for first-aid treatment of subsequent reactions.³ Thus, adrenaline data provide a novel and practical approach for studying and monitoring the epidemiology of anaphylaxis in the community.⁴

The aim of the present study was to evaluate the dispensing rate of adrenaline in Israel over the last 8 years compared with other countries.

Methods

Data on the number of adrenaline injectors (EpiPen 0.3 mg and EpiPen Jr 0.15 mg) dispensed each year from 1997 to 2004 were derived using Business Objects software (1990) from the database of the Purchase Department, Division of Logistics and Infrastructure of the General Health Services (Clalit), which is the largest of the four health maintenance organizations in Israel, serving about 60% of the country's population. Data on mortality associated with anaphylaxis and asthma from 1998 to 2000 were derived from the Central Bureau of Statistics, Jerusalem, using the new codes of the International Classification of Diseases, 10th revision (ICD-10): T78.0 (anaphylactic shock due to adverse food reaction); T78.2 (anaphylactic shock, unspecified); X23 (contact with hornets, wasps and

bees); and J45 (asthma), J46 (status asthmaticus) (data from 2001 to 2003 are not yet available).

Results

Table 1 shows the number of EpiPen and EpiPen Jr units dispensed to patients each year from 1997 to 2004 by the General Health Services. The total dispensing rate of EpiPen units increased by 76% over the 8-year period; the dispensing rate of EpiPen 0.3 mg increased by 89%, and that of EpiPen Jr 0.15 mg increased by 59%. Considering that 60% of the Israeli population is insured by the General Health Services, the increased dispensing rate of EpiPen units most likely represents a true increase in the national population (6 million inhabitants) for a rate of 83 units dispensed per 100 000 inhabitants in 2004 (0.083%).

According to data from the Central Bureau of Statistics, there were no reported deaths from anaphylaxis or insect stings from 1998 to 2000, and 137 reported deaths from asthma.

Discussion

The present study revealed an almost two-fold increase in the overall dispensing rate of EpiPen units from 1997 to 2004. The increase in the dispensing rate was considerably higher for EpiPen 0.3 mg than for EpiPen Jr 0.15 mg (89% vs. 59%). This difference is probably due to the exclusive use of the EpiPen Jr by children aged less than 8 years and weighing 15–28 kg. This group is characterized by fewer life-threatening anaphylactic reactions than older groups, although they have a higher prevalence of food allergy.⁵

The true incidence of anaphylaxis is unknown. Researchers suspect that it is often under-reported or misdiagnosed due to its similarity to other conditions.^{6,7} Based on prevalence estimates of each of the four main causes of anaphylaxis (food, drugs, latex and insect stings), Neugut et al.⁷ calculated that 1.21–15.04% of the population in the USA are at risk. Several population-based

Table 1 Number of EpiPen units dispensed between 1997 and 2004.

	1997	1998	1999	2000	2001	2002	2003	2004
EpiPen 0.3 mg	1343	1426	1817	1668	1673	2161	2278	2432
EpiPen Jr 0.15 mg	346	417	321	516	420	563	548	549
Total	1689	1843	2138	2184	2093	2724	2826	2981

Table 2 Epidemiology of anaphylaxis.

Reference	Country	Incidence of anaphylaxis
Yocum et al. ¹¹	USA	21/100 000 person years
Helbling et al. ⁸	Switzerland	8.9/100 000/year
Bohlke et al. ⁹	USA	10.5/100 000 person years
Peng et al. ¹⁰	UK	8.4/100 000 person years

studies have investigated the occurrence of anaphylaxis in different countries (Table 2); three reported an incidence of 9–10/100 000 person-years,^{8–10} and one found a rate of 21/100 000 person-years.¹¹

Simons et al.⁴ used the dispensing patterns of self-injectable adrenaline as a surrogate marker of anaphylaxis in the general population of Manitoba province, Canada (population 1.15 million). They found that over a 5-year period, 0.95% of all residents had been prescribed the EpiPen at least once for home treatment. Accordingly, the rate of anaphylaxis in the community was similar to that noted in the study of Yocum et al.¹¹ In a study from Australia based on EpiPen units provided to pharmacies and hospitals for use by children less than 10 years of age, Kemp⁵ reported an increase of 300% over a 5-year period for a crude prescription rate of 1/544 children. The total dispensing rate for EpiPen units (children and adults) increased by 193%.

The present study was unable to differentiate between the different age groups to which EpiPen was dispensed, and it was not possible to document how many times EpiPen was dispensed to a single person, as in the study of Simons et al.⁴ Therefore, the almost two-fold increase over 8 years may be an overestimation. Nevertheless, the rate found in this study is still lower than the two- to three-fold increase over 5 years in Australia.⁵ The rates per population found in the present study are also considerably lower than the 1% reported by Simons et al.⁴ These differences may be explained by the reluctance of primary care physicians in Israel to prescribe adrenaline without consulting an allergist (Y. Levy, personal communication).

Israel has no national registry of anaphylaxis. Data on allergic reactions to insect stings (collected in 10 000 13–14-year-old children by self-reported questionnaire) revealed that 11.5% of affected children had a large local reaction, 6.5% had a mild systemic reaction, and 2.5% had a severe systemic reaction. These rates are higher than estimated previously.¹²

Anaphylaxis can be misdiagnosed as a severe or even fatal asthma exacerbation, especially in

patients with food allergy.^{13,14} The prevalence of asthma in Israel in 1997 in children aged 13–14 years was found to be 7.8% for Jewish children and 4.9% for Arab children, with corresponding rates of 20.7% and 10.1% for current wheeze.¹⁵ Among 94 805 17-year-old conscripts to the Israel defence forces, 8% of men and 6.8% of women had a known diagnosis of asthma, of whom 50% had moderate to severe disease.¹⁶ Picard et al.¹⁷ calculated that the mean mortality rate for asthma in Israel between 1980 and 1997 in patients aged 5–34 years was 0.226/100 000 population, without significant changes over the years (100 asthma mortality cases were reported during this period). Most of the patients died outside the hospital. Furthermore, a recent study from northern Israel demonstrated a significant increase in first-time hospital admissions for asthma in children over a 10-year period (1990–1999).¹⁸

In the present study, analysis of data from the Central Bureau of Statistics from 1998 to 2000 (data for 2001–2003 are still unavailable) yielded 137 deaths associated with a diagnosis of asthma (ICD-10: J45) or status asthmaticus (ICD-10: J46). This rate is higher than the reported Israeli rates for 1995–1997 and 1992–1994,¹⁷ most probably because the age in the latter study only ranged from 5 to 34 years. The lack of reported cases of fatal food- and insect-sting-induced anaphylaxis may indicate underdiagnosis, under-reporting or misdiagnosis of some cases as fatal asthma.

Kemp⁵ claimed that the rapid increase in EpiPen use (which is not devoid of side effects) is not primarily due to the known increase in allergic diseases, but rather the combination of increased community concern and increased awareness of anaphylaxis. He suggested that six factors should be taken into consideration by clinicians before prescribing the EpiPen: age over 5 years; history of respiratory tract involvement; history of asthma; peanut or tree nut allergy; reaction induced by small amounts of allergen; and strongly positive skin test. Nevertheless, it is well recognized that the course of anaphylactic episodes cannot be predicted with certainty, and it may differ from person to person and from one episode to another in the same person. Furthermore, early use of adrenaline in anaphylaxis is associated with improved outcome.¹⁹ It is now accepted worldwide that any patient with a systemic allergic reaction should be considered a candidate for adrenaline. The prescription of auto-injectors needs to be targeted particularly at patients with asthma and systemic allergic reactions.³

In summary, the data on EpiPen dispensing to the general population in Israel demonstrates a

substantial increase over the last 8 years, but is still less than that reported in other countries. Recent studies demonstrated that the rate of self-reported allergic reactions to insect stings in children is high (approaching that of adults in other studies), and the rate of admissions due to asthma in children in Israel has increased. However, there were no reported cases of anaphylactic death. Therefore, it can be assumed that the increase in the dispensing rate of EpiPen units is mainly attributable to an increased awareness of the potential fatal outcome of anaphylactic reactions and indication for treatment among physicians and patients, in accordance with the clinical guidelines worldwide. However, it may also be partly explained by underdiagnosis and under-reporting.

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