

Epinephrine dispensing patterns for an out-of-hospital population: A novel approach to studying the epidemiology of anaphylaxis

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Background: The underlying rate of occurrence of anaphylaxis from all potential triggers in the general population is unknown.

Objective: We sought to obtain a perspective on the epidemiology of anaphylaxis in a defined general population by studying epinephrine dispensing patterns in an out-of-hospital setting.

Methods: Using an administrative claims pharmaceutical database, we analyzed dispensing data for all epinephrine formulations prescribed for out-of-hospital treatment over 5 consecutive fiscal years in a population of 1.15 million persons in the province of Manitoba, Canada. We identified the number and percentage of individuals in the general population for whom epinephrine was dispensed on one or more occasions, their age and sex, and the type of formulation dispensed. In addition to performing these analyses for the entire population of children, adults, and elderly individuals, we also performed analyses by 5-year age groupings; furthermore, for individuals younger than 5 years of age, we performed a detailed analysis by 6-month age groupings.

Results: During the 5-year period, 0.95% of this defined general population had injectable epinephrine dispensed for out-of-hospital treatment. There were substantial variations in epinephrine dispensing rates across subsets of the population, ranging from 1.44% for individuals younger than 17 years of age, to 0.9% for individuals 17 to 64 years of age (inclusive), to 0.32% for those age 65 years or older. In infancy, childhood, and early adolescence boys were more likely to have epinephrine dispensed than girls. Beginning at age 15 years and continuing into adulthood, girls and women were more likely to have epinephrine dispensed than boys and men. In the elderly there were no differences in dispensing patterns between the

sexes. The highest epinephrine dispensing rate (5.3%) was found for boys age 12 to 17 months.

Conclusions: Epinephrine dispensing data provide a novel and practical approach for studying and monitoring the epidemiology of anaphylaxis in a community. Using this approach, we provide evidence that anaphylaxis from all triggers peaks in early childhood and then gradually declines into old age. (*J Allergy Clin Immunol* 2002;110:647-51.)

Key words: Epinephrine, adrenaline, anaphylaxis, severe acute allergic reactions, general population, EpiPen, EpiPen Jr, Ana-Kit, food allergy, Hymenoptera venom allergy, latex allergy, drug allergy

Systemic anaphylaxis is a rapidly progressive, potentially life-threatening, severe acute allergic reaction with many potential specific trigger factors, such as foods, insect venoms, latex rubber, medications, vaccines, and exercise.^{1,2} It occurs more commonly in a community setting than in a health care setting.¹

The true rate of occurrence of anaphylaxis from all triggers is unknown. In a recent medical literature review, it was stated that anaphylaxis from the 4 most common triggers (foods, latex rubber, insect venoms, and medications) was not as rare as is generally believed and that more than 1% of the US population might be affected.² In the only study to date in which the occurrence rate of anaphylaxis from all triggers has been investigated in a defined general population, it was identified retrospectively as being less than 1%.³ In the epidemiologic studies of anaphylaxis from all triggers which have focused on selected subpopulations such as patients in allergy clinics,⁴⁻⁹ hospital emergency departments,¹⁰⁻¹⁴ hospital inpatient units,¹⁵⁻¹⁷ or morgues,¹⁸ rather than the general population, anaphylaxis was reported to be uncommon but increasing.^{16,17}

The standard of care for patients with a history of anaphylaxis that has occurred in nonmedical settings is prescription of self-injectable epinephrine for first-aid treatment of subsequent reactions.¹ Moreover, a history of anaphylaxis is the only approved indication for prescribing and dispensing epinephrine in the form of EpiPen, EpiPen Jr, and Ana-Kit for out-of-hospital use. We therefore hypothesized that a novel perspective on the epidemiology of anaphylaxis in the general population could be obtained by studying epinephrine dispensing patterns for an entire population in an out-of-hospital setting.

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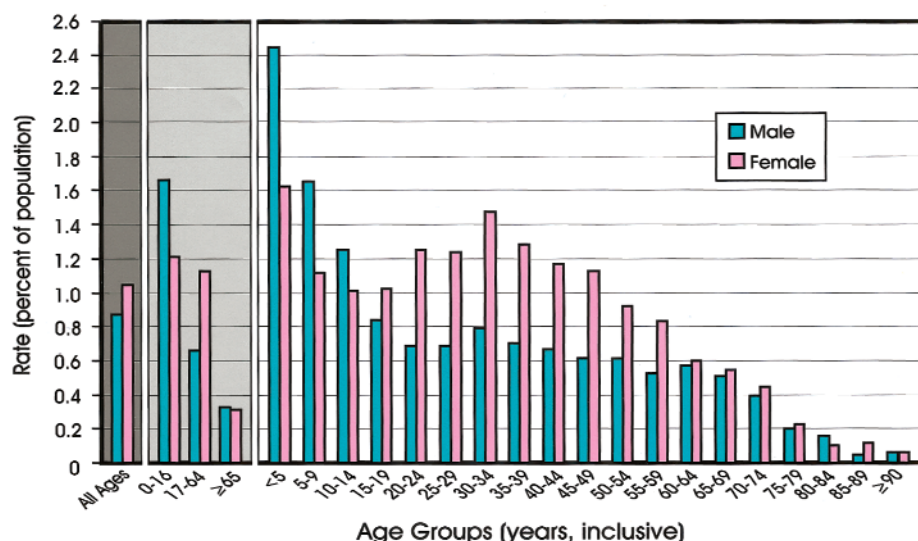


FIG 1. Epinephrine dispensing for out-of-hospital treatment. Epinephrine dispensing rate versus sex and age plotted for the entire population, for 3 arbitrarily selected age groups (infants, children, and adolescents <17 years of age, individuals 17-64 years of age [inclusive], and elderly individuals ≥65 years of age), and by 5-year age groupings for the entire population. Note the relatively high rate of epinephrine dispensings for young boys compared with that for young girls and for middle-aged women compared with that for middle-aged men.

METHODS

We used the University of Manitoba Health Research Database, which is derived from computerized information systems that support the provision of insured medical services in the province of Manitoba. These information systems incorporate the Drug Program Information Network, an administrative claims pharmaceutical database that comprehensively tracks prescriptions dispensed out of hospital under the provincially insured drug benefits program for the 1.15 million residents in the province. The Drug Program Information Network contains patient-level data provided by real-time computer links with all retail pharmacies in the province. The anonymized University of Manitoba Health Research Database has been shown to be complete and valid for clinical and outcome studies^{19,20} and has been previously used for a comprehensive community-based 4-year study of the types of epinephrine formulations dispensed for infants and children at risk for episodes of anaphylaxis.²¹

To ascertain the rates of epinephrine dispensing, we analyzed dispensing data for all epinephrine formulations, excluding topical ophthalmic formulations, prescribed for out-of-hospital treatment over 5 consecutive fiscal years, from April 1, 1995, to March 31, 2000. We identified the number and percentage of individuals in the general population for whom epinephrine was dispensed on one or more occasions during this period, their age and sex, and the specific epinephrine formulation dispensed. For calculation of percentages and rates, these individuals were assigned to their age on the day when they were first dispensed epinephrine during the 5 years of observation. In our person-based analysis, an individual was counted only once during the entire 5-year period, even if he or she received more than one epinephrine dispensing. The denominator for the percentage and rate calculations was the population of Manitoba on December 31, 1999. The age of the population was also assigned as of December 31, 1999. To test the reproducibility of our results, we conducted a second set of analyses in which we restricted our observations to the smaller number of individuals who received 2 or more epinephrine dispensings during the study period.

In addition to performing these analyses for the entire population and for individuals younger than 17 years of age, individuals 17 to 64 years of age (inclusive), and elderly persons age 65 years and older, we performed analyses by 5-year age groupings; furthermore, for individuals younger than 5 years of age, we performed a detailed analysis by 6-month age groupings.

This project was approved by the University of Manitoba Research Ethics Board and by the Access and Confidentiality Committee of Manitoba Health and was conducted in accordance with legislation protecting the privacy of Manitoba residents.

RESULTS

During the 5 years of the study, there were, on average, 278,757 Manitoba residents younger than 17 years of age, 710,192 residents 17 to 64 years of age (inclusive), and 155,539 residents 65 years of age or older. The types of epinephrine formulations that were dispensed for use out of hospital were as follows: 68.5% EpiPen, 17.2% EpiPen Jr, 13.2% Ana-Kit, and 1.1% ampules of epinephrine for injection, EZ Pen, or other formulations.

Our estimate of the overall rate of anaphylaxis for the entire Manitoba population, as measured by having one or more epinephrine prescriptions dispensed for out-of-hospital use, was 954 per 100,000 persons (0.95%). This was based on a total of 10,949 persons for whom epinephrine was dispensed during the 5-year study period, of whom 6415 (58.6%) received only one epinephrine dispensing, 2446 (22.3%) received 2 dispensings, and 2088 (19.1%) received 3 or more dispensings.

Epinephrine dispensing rates were highest (1.44%) for individuals who had not yet reached their 17th birth-

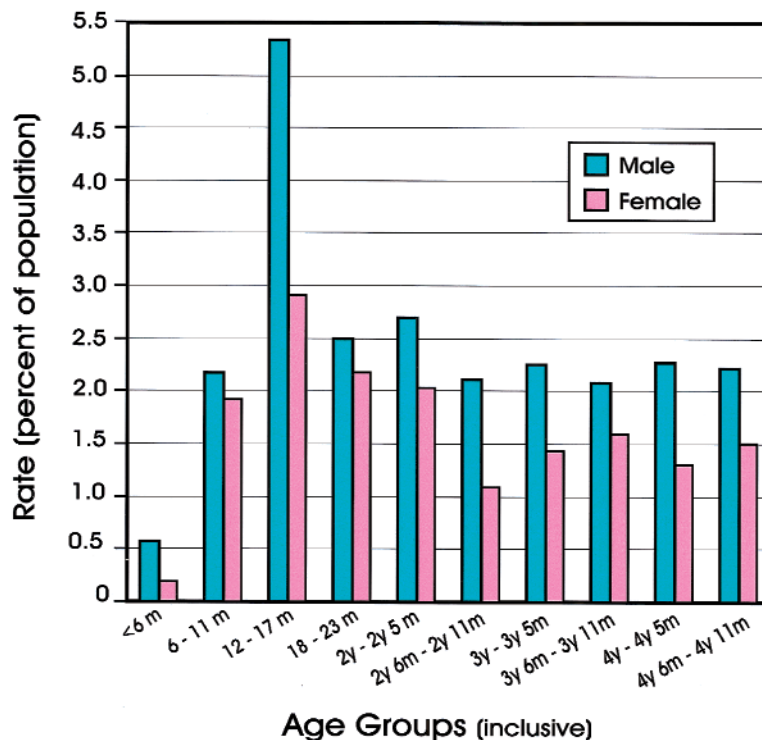


FIG 2. Epinephrine dispensing for individuals younger than 5 years of age, plotted by 6-month age groupings. The dispensing rate was higher for boys than for girls, with an almost 2-fold difference at age 12 to 17 months (inclusive). *m*, Months; *y*, years.

day, 0.9% for those age 17 to 64 years (inclusive), and 0.32% for those age 65 years or older (Fig 1). Using a more detailed breakdown by 5-year age groupings, we found that the epinephrine dispensing rate peaked for individuals younger than 5 years of age and remained relatively high until age 40 years, after which it gradually declined (Fig 1). Although the epinephrine dispensing rate was low (0.4%) for infants under the age of 6 months, it was 2% for those age 6 to 11 months (inclusive) and 4% for those age 12 to 17 months (inclusive; Fig 2). All of these patterns remained intact in a second set of analyses, in which we restricted our numerator to the subset of individuals who had received 2 or more epinephrine dispensings during the 5-year study period (4534 individuals or 41.4% of all those for whom epinephrine was dispensed).

Overall, epinephrine was dispensed more commonly for females (1.0%) than for males (0.86%; Fig 1). In childhood and in adolescents younger than 15 years of age, boys were more likely to have epinephrine dispensed than girls. In adolescence, beginning at age 15 years and continuing into adulthood, girls and women were more likely to have epinephrine dispensed than boys and men (Fig 1). In the elderly there was no difference in epinephrine dispensings between the sexes. The highest rate of epinephrine dispensing, 5.3%, occurred for boys age 12 to 17 months (Fig 2).

DISCUSSION

Epidemiologic studies of “all-triggers” anaphylaxis, whether retrospective or cross-sectional, have been hampered by the lack of a consistent definition of anaphylaxis and, until 1999, by the lack of an official diagnostic code for anaphylaxis or anaphylactic shock in the International Classification of Diseases.² In addition, although the majority of episodes of anaphylaxis occur outside of a hospital or health care setting, most epidemiologic studies of anaphylaxis from all triggers have been based in health care settings,⁴⁻¹⁸ rather than in the general population,³ and most of the studies have involved relatively small numbers of patients.^{4-15,18}

Here we report an innovative approach to ascertaining the occurrence rate of anaphylaxis in a defined general population of 1.15 million persons that is based on using dispensing patterns of self-injectable epinephrine as a surrogate marker for anaphylaxis. This approach ensures that we have captured epinephrine dispensings for the out-of-hospital treatment of anaphylaxis from all trigger factors, not just specific trigger factors such as foods, insect venoms, latex rubber, or medications, and from all prescribing physicians, not just allergists or emergency department physicians. Using this novel approach, we have estimated the occurrence rate of anaphylaxis in the community to be 0.95%. This ratio is similar to that

reported in the only previously published epidemiologic study of anaphylaxis from all triggers in an entire community,³ in which a retrospective review of medical records was used to identify 133 patients with anaphylaxis in a county population of 1255 residents. In this retrospective study the investigators commented that this "is surely an under-estimate because anaphylaxis is frequently unrecognized and undiagnosed by physicians, and milder episodes, although potentially fatal, do not prompt patients to seek medical care."³

We found that although nearly 1% of the general population had epinephrine dispensed on one or more occasions during 5 years, there were substantial variations in the dispensing rates across subsets of the population. These ranged from 1.44% for children and adolescents younger than 17 years of age, with a 10-fold variation (from 0.4 to 4%) within this age group, to 0.9% for individuals 17 to 64 years of age (inclusive) and to 0.32% for elderly persons 65 years of age or older. These data suggest that anaphylaxis is more likely to be recognized and treated in childhood and early adolescence than in adulthood. The differences in dispensing rates might either reflect age and sex bias in epinephrine prescribing and dispensing patterns, as reported for other classes of medications,^{19,22} or they might reflect a true difference in anaphylaxis occurrence, as evidenced in a recent pediatric study in which real-time reporting of anaphylaxis from all triggers revealed that 60% of the episodes occurred in boys, predominantly in preschoolers.²³

The high occurrence rate of anaphylaxis in the pediatric population relative to the adult population, identified here for the first time, is consistent with the relatively high occurrence rates for related disorders, such as asthma, allergic rhinitis, and atopic dermatitis, in young persons.²⁴ In this regard our study population differs from those described in previous community,³ allergy clinic,^{5-7,9} emergency department,^{10,11,13} hospital,^{16,17} and morgue¹⁸ studies of all-triggers anaphylaxis involving patients of all ages, in which the mean age of the patients ranged from 29 years³ to 52 years,¹⁸ and female patients generally predominated.

It is possible that the occurrence rate of anaphylaxis ascertained indirectly from epinephrine dispensing data might have been overestimated in the present study. Some dispensings might have been made as a precautionary measure,²⁵ in case a patient's symptoms turned out to be a harbinger of anaphylaxis. Also, although certainly not the usual practice in Manitoba during the time of the study, a physician might have, on occasion, prescribed epinephrine on the basis of allergen sensitization, as evidenced by a positive skin test or in vitro test result, in the absence of a clear history of anaphylaxis.²⁶

It is also possible that the occurrence rate of anaphylaxis ascertained indirectly from epinephrine dispensing data might have been underestimated in this study. The most important physician-related factor potentially contributing to low epinephrine prescription and dispensing rates involves lack of recognition of anaphylaxis, specifically failure to diagnose anaphylaxis in the absence of fully

developed shock and subsequent failure to prescribe epinephrine for first-aid treatment of future episodes.^{3,10} This is a concern in view of recent documentation that 44% to 59% of patients presenting initially with a mild, non-life-threatening allergic reaction might have a severe, potentially life-threatening reaction after subsequent inadvertent exposure to the same trigger.^{27,28} In addition, physicians identifying iatrogenic anaphylaxis triggered by medications, vaccines, or biologic agents in a hospital or other health care setting probably would not have prescribed epinephrine for first-aid use by such patients in the community.¹

Patient-related (and, for children, parent- or caregiver-related) factors might also have potentially contributed to underdiagnosis of anaphylaxis, low dispensing rates for epinephrine, and underestimation of the occurrence rate of anaphylaxis. Patients who failed to recognize the significance of mild or moderate anaphylaxis symptoms, recovered spontaneously, were not evaluated by a physician, and never received an epinephrine prescription from a physician would not be included in our epinephrine dispensing data. Because the extent of unrecognized anaphylaxis in the population is unknown, this effect might be quite large. Smaller effects potentially leading to underestimates in our epinephrine dispensing data might be due to patients who received an epinephrine prescription from a physician but did not follow through to acquire the medication, or to patients who died during a first episode of anaphylaxis that occurred between April 1, 1995, and March 31, 2000 (inclusive), and never had epinephrine dispensed for outpatient use.

In summary, our research suggests that almost 1% of the population might be at risk of anaphylaxis, as defined by having injectable epinephrine available for out-of-hospital use. This estimate is comparable with the only other report of all-triggers anaphylaxis in a defined general population.³ Although our approach might have led to overascertainment or, like in the previous report,³ to underascertainment of individuals at risk for anaphylaxis in the community, it provides a unique method of estimating the occurrence rate of anaphylaxis from all triggers in the general population. The potential for using epinephrine dispensing data as a practical method for studying and monitoring the epidemiology of anaphylaxis from all triggers in the general population will be enhanced in years to come, when these data can be linked with the precise International Classification of Diseases 10 diagnostic coding for anaphylaxis which has recently become available.²

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