

## Unintentional Therapeutic Errors Involving Insulin in the Ambulatory Setting Reported to Poison Centers

Henry A Spiller, Douglas J Borys, Mark L Ryan, Tama S Sawyer, and Brooke L Wilson

Adverse drug events in the ambulatory care setting are not uncommon and can cause significant morbidity.<sup>1-4</sup> Insulin is one of the leading medications involved in adverse drug events leading to an emergency department visit, especially in older adults.<sup>2</sup> However, the published data on insulin adverse drug events have focused primarily on the hospital setting.<sup>1-4</sup> There is a lack of information on the epidemiology of insulin-associated adverse drug events in the ambulatory care or non-hospital-based setting. One study of a poisons unit in Germany found that 5% of insulin overdoses were accidental, and 90% of the cases were intentional suicidal insulin overdose, with all inquiries coming from the physician caring for the patient, suggesting these cases were not being managed in the ambulatory setting.<sup>5</sup>

In the US, poison control centers are able to manage the majority of their patients in the ambulatory care setting, often reducing the need for an unnecessary emergency department visit.<sup>6,7</sup> Poison control centers manage more than 200,000 adverse drug events annually, with 88% of these patients managed outside of the hospital setting.<sup>3,7</sup> The real-time database of these centers would be

**BACKGROUND:** Adverse drug events in the ambulatory care setting are not uncommon and can cause significant morbidity. Little research has been published on the management of adverse drug events involving insulin in the outpatient setting.

**OBJECTIVE:** To analyze data on patients with unintentional therapeutic errors involving insulin managed by 9 regional poison control centers.

**METHODS:** A retrospective search was performed for all records involving insulin at 9 poison centers, covering the population of 4 states for the years 2000-2009. A subgroup of the study population was selected with a reason for exposure of “unintentional—therapeutic error.”

**RESULTS:** There were 3819 insulin exposures reported, with an increase in the annual incidence of insulin exposures of 279% (from 170 to 645 patients/year) and a mean annual increase of 18%. Of the insulin exposures, 2584 were unintentional therapeutic errors (68%). The percentage of all insulin exposures that were unintentional therapeutic errors increased progressively, from 41% to 78%. There was a 495% increase in annual incidence of unintentional therapeutic errors involving insulin, with a mean annual increase of 28%. Unintentional therapeutic errors involving insulin occurred primarily in adults >40 years (73%), with 63% occurring in women. There was a pronounced increase in unintentional therapeutic errors involving insulin in the later evening hours, with 71% occurring between 1800 and 2400 and reaching a peak at 2200. The majority (n = 1803; 70%) of patients were managed in a non-health-care facility location, primarily their own residence.

**CONCLUSIONS:** This is the first report of an increasing trend of insulin-related unintentional therapeutic errors in the ambulatory setting. Our study highlights a number of striking features, including: (1) a consistent and dramatic increase of unintentional therapeutic errors involving insulin over the 10-year period, (2) a high incidence of unintentional therapeutic errors involving insulin in the late evening hours, and (3) a high incidence of unintentional therapeutic errors involving insulin involving adults >40 years and females. With their 24/7 availability, poison centers appear to be an increasingly important resource for patients experiencing unintentional therapeutic errors involving insulin.

**KEY WORDS:** adverse drug event, ambulatory care, insulin, poison center, therapeutic error.

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a rich source of information on insulin adverse drug events in the ambulatory care setting. To date, no information has been published evaluating insulin adverse drug events in this setting. The objective of this study was to delineate characteristics and outcomes of unintentional therapeutic errors involving insulin, with a focus on cases in the ambulatory care setting.

## Methods

A retrospective search was performed for all records involving insulin at 9 poison centers, covering the population of 4 states (36.4 million people) for 2000-2009. The 9 centers were the Kentucky Regional Poison Control Center, the Louisiana Poison Center, the 6 poison centers comprising the Texas Poison Control Network, and the University of Kansas Hospital Poison Control Center. All 9 poison centers use the electronic medical record system Toxicall.

To identify the study group of human exposures involving insulin, a search was performed using the American Association of Poison Control Centers (AAPCC) generic code for insulin (0236000). Identification of the individual insulin types was not part of the data obtained, but all insulin exposures were included. The data were obtained for each year, 2000 through 2009, for each center. Single-substance and poly-substance exposures were included. Exclusion criteria included animal exposures and drug or poison information calls not involving an exposure. Time of day data were determined by the time of day of first contact with the poison center on each particular case (ie, when the patient first sought contact for medical assistance).

A subgroup of all human exposures involving insulin was chosen for separate evaluation: patients with an unintentional therapeutic error involving insulin. All poison center exposure calls have a reason for the exposure assigned from a list of preestablished categories. This reason is assigned by the specialist (usually a pharmacist or nurse) managing the case at the poison center at the time of occurrence. The AAPCC defines "unintentional—therapeutic error" as "an unintentional deviation from a proper therapeutic regimen that results in the wrong dose, incorrect route of administration, administration to the wrong person or administration of the wrong substance."<sup>7</sup> This group was selected to capture the adverse drug events based on patient error or resulting from patient error. Adverse events occurring because of a reaction to the drug would be coded separately by a poison center as "Adverse Reaction—drug." A subsequent analysis was performed on the subgroup of patients with an unintentional therapeutic error involving insulin. All information was provided to the investigators in tabular form, devoid of all personal health information. Data obtained included age, sex, location of patient management, medical outcome, and time of day of

occurrence. The definitions for medical outcome were standard AAPCC definitions and are defined as no effect (no signs or symptoms as a result of the exposure), minor effect (signs or symptoms were minimally bothersome and resolved rapidly, eg dizziness), moderate effect (signs or symptoms were more pronounced, more prolonged, or more systemic in nature but did not require specific intervention, eg, hyperactivity, sinus tachycardia, moderate hypertension), major effect (signs or symptoms were life-threatening or required specific intervention, eg, seizures), or death (death resulted from the exposure or direct complication of the exposure).<sup>7</sup> Patient management site is a predesignated AAPCC category that refers to where the patient received care, if any, including care at home (eg, additional meal for caloric intake) as well as care at a health-care facility involving direct medical evaluation and treatment.<sup>7</sup>

Additionally, the raw count/total number of (1) all human exposures reported to the 9 poison centers and (2) all patients with an unintentional therapeutic error (all drug categories) were obtained from each center for each year of the study. This allowed a comparison between the change in unintentional therapeutic error rates for all drugs and the unintentional therapeutic error rates involving insulin.

Statistical analysis, because of the retrospective nature of the data, is descriptive. Linear regression and  $\chi^2$  test for trend was used to evaluate changes in annual rates of all human exposures (all substances), unintentional therapeutic errors for all substances, and unintentional therapeutic errors involving insulin.

## Results

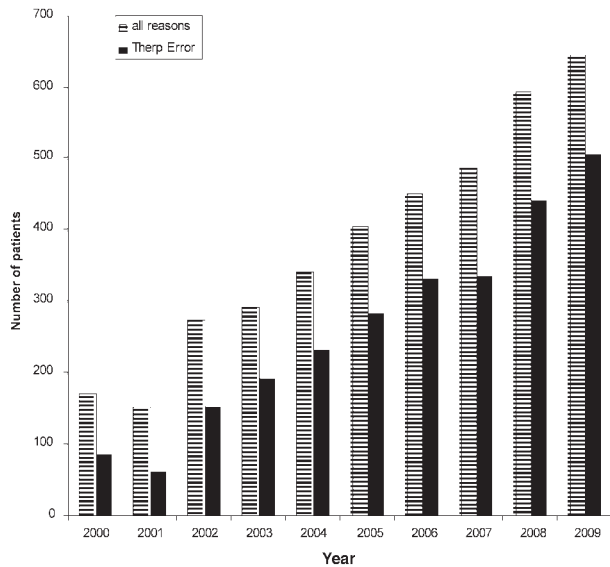
From 2000 through 2009, 3819 insulin exposures were reported to the 9 poison centers. There was an increase in the annual incidence of insulin exposures of 279% reported in the 10-year period, from 170 patients in 2000 to 645 patients in 2009, with a mean annual increase of 18% (Figure 1). The increase in annual incidence of insulin exposures was consistently explained by the increase in unintentional therapeutic errors involving insulin. There were 2584 unintentional therapeutic errors involving insulin (68%). The percentage of all insulin exposures that were unintentional therapeutic errors increased progressively, from 41% to 78%. There was a 495% increase in annual incidence of unintentional therapeutic errors involving insulin, with a mean annual increase of 28% (Figure 1).

The annual increases seen in the unintentional therapeutic errors involving insulin were not simply a reflection of changes in the number of total patients managed by the 9 poison centers ( $p > 0.05$ ). The increase in total human exposures over the 10 years was 16.7%, with a mean annual increase of 5.51%. There was a significant linear correla-

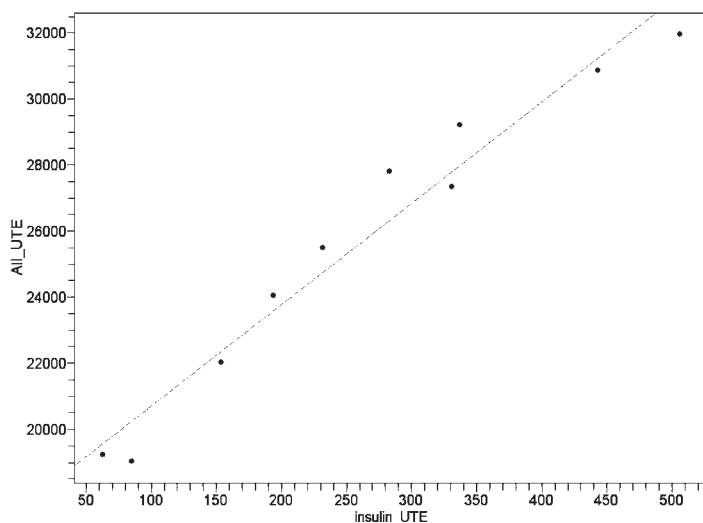
tion between the annual number of unintentional therapeutic errors (all drug categories) and the annual number of unintentional therapeutic errors involving insulin ( $p < 0.05$ ) (Figure 2). However, when analyzing the group of patients with unintentional therapeutic errors for all substances, the proportion of unintentional therapeutic errors involving insulin increased 281%, from 0.4% to 1.6% ( $p < 0.05$ ) (Figure 3).

The remaining analysis is restricted to the group of unintentional therapeutic errors involving insulin. Unintentional therapeutic errors involving insulin occurred primarily in older adults, with 73% of such patients  $>40$  years old (Fig-

ure 4). The majority of patients with unintentional therapeutic errors involving insulin were female ( $n = 1631$ ; 63%). While unintentional therapeutic errors involving insulin occurred throughout the day, there was a pronounced increase in the later evening hours, with 71% occurring between 1800 and 2400, reaching a peak at 2200 (Figure 5). The majority ( $n = 1803$ ; 70%) of patients were managed in a non-health-care facility location, primarily their own residence. The percentage of patients managed in a non-health-care facility did not change over the 10-year period (range 68-73%) despite the increase in the number of patients. This is likely because more than half of patients had either no effect or a minor effect from the insulin exposure (Figure 6). There were 299 moderate medical outcomes (12%), 10 major outcomes ( $<1\%$ ), and no deaths. All of the 10 major medical outcomes were ultimately managed in a health-care facility.



**Figure 1.** Annual incidence of all insulin exposures and unintentional therapeutic (Therp) errors involving insulin.



**Figure 2.** Comparison of annual rate of unintentional therapeutic errors (all drug categories; All\_UTE) with annual rate of unintentional therapeutic errors involving insulin (insulin\_UTE).

### Discussion

To our knowledge, no previous study has reported the frequencies and characteristics of insulin-related unintentional therapeutic errors in the ambulatory setting. This is the first study looking specifically at unintentional therapeutic errors secondary to insulin reported to poison centers. Our study highlights a number of striking features, including (1) a consistent and dramatic increase of adverse events over the 10-year period, (2) a high incidence of adverse events in the late evening hours, and (3) a high incidence of adverse events involving adults  $>40$  years.

The increase in incidence is not entirely unexpected. The proportion of the US population with diabetes is on the increase and expected to nearly double over the next 25 years.<sup>8</sup> Additionally there has been an increase in the use of insulin therapy in type 2 diabetes, increasing the population that uses insulin daily.<sup>9,10</sup> This increased use of insulin and increasing population with diabetes may be factors in the increased unintentional therapeutic errors involving insulin found in our study. It is unclear from our data whether the significant increase occurred solely because there was an increased number of unintentional therapeutic errors involving insulin, whether an increased number of patients with therapeutic errors involving insulin are using a poison center for help, or a combination of these factors. However, the consistent and nearly 3-fold increase over 10 years suggests that this area may warrant further research. Other areas for further research might include the types of insulin involved in unintentional therapeutic errors involving insulin and whether the type of insulin affected outcomes.

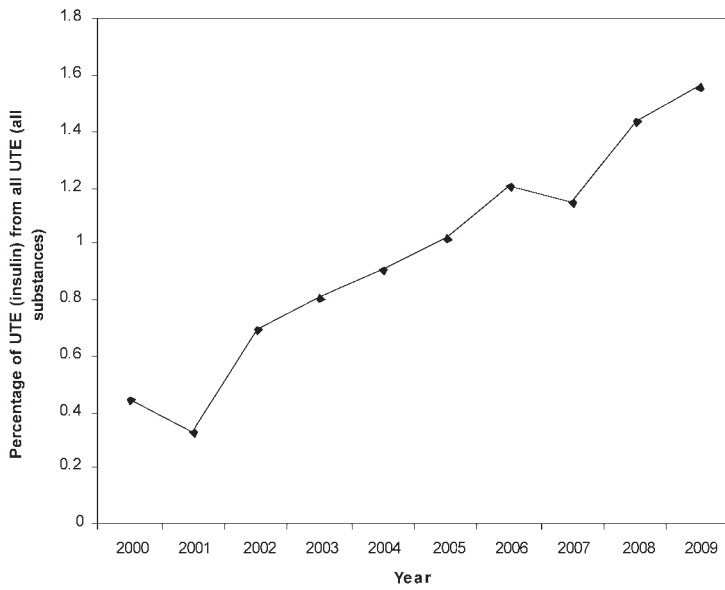
The increased incidence of unintentional therapeutic errors in the later evening hours is likely related to the multiple dosing regimens associated with insulin. Diabetic patients with insulin requirements often face a variable regimen of different types of insulin and insulin doses throughout the day, based on meal times and activity levels. Our study suggests that adverse events involving insulin based on patient error are far more common in the evening, when there is often a change in dosage and/or type of insulin from daytime use. It is unknown whether the number of cases reported to a poison center during the daytime hours was affected by patients having other re-

sources available during the day, such as a physician's office or clinic. Such an effect, if it were to occur, would skew the poison center data toward more patients in the evening hours. Information from this study may be helpful in creating patient education materials to potentially reduce future incidents of adverse events.

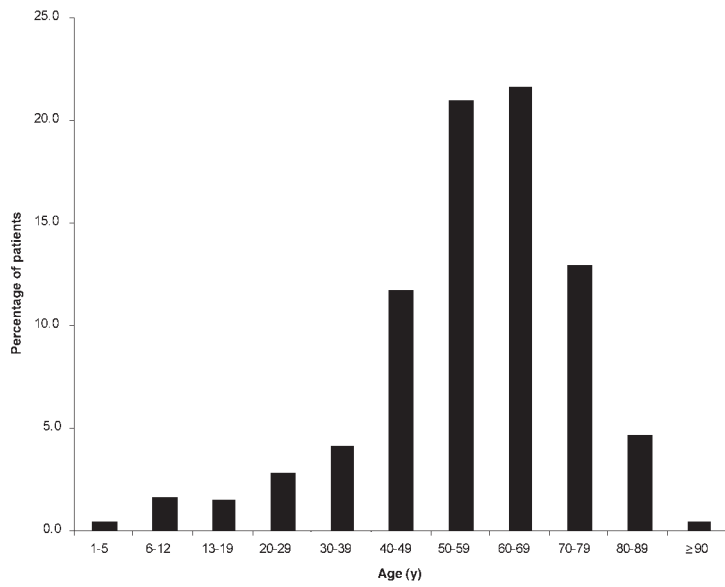
Another important feature noted in this study was that 70% of these patients were able to be managed outside of a health-care facility, one of the hallmarks of the US poison center system.<sup>6,11</sup> Because the time of occurrence of the majority of these unintentional therapeutic errors was the late evening, the choice of resources available to these

patients is often limited. Primary care facilities such as a physician's office or clinic are closed and not routinely available. Poison centers, with their availability at all hours and staff of trained health-care professionals, appear to be an increasingly important resource for patients with an adverse event involving insulin. With the expected increase in the prevalence of diabetes and the use of insulin, this is likely to continue to be an important service provided by poison centers, as adverse drug events involving insulin are not without serious risk, including hypoglycemia and hypoglycemia-associated complications such as coma, seizure, hypotension, and neurologic injury. Twelve percent of the patients in this study experienced more prolonged systemic effects (moderate and major effects) that would include effects greater than a simple change in blood glucose level. Changes in mental status (eg, confusion, coma) are particularly worrisome, as they could incapacitate the individual, making him or her unable to obtain help or take actions to raise the blood glucose level. Patient education efforts should include recommendations that the patient have another adult or caregiver immediately available in the event that mental status changes occur.

We believe the increased incidence of unintentional therapeutic errors involving insulin in adults >40 years is likely a reflection of the population with diabetes as well as the increased use of insulin in the population with type 2 diabetes. The estimated prevalence of diabetes increases with age, from an estimated 2.6% prevalence in the 20- to 39-year age group, to 10.7% in the 40- to 59-year age group, to 23% in the >60-year age group.<sup>12</sup> A second demographic feature, however, was unexpected. Diabetes is slightly more prevalent in males than in females (11.2% vs



**Figure 3.** Percentages of unintentional therapeutic error (UTE) involving insulin rates by year.



**Figure 4.** Age of patients with an unintentional therapeutic error involving insulin.

10.2% of population).<sup>10</sup> In patients using a poison center for unintentional therapeutic errors involving insulin, the shift was pronounced, with 63% females and 37% males. It is unclear whether this reflects a higher incidence of unintentional therapeutic errors in females or rather a higher use of poison centers by females, or a combination of the two.

There are a number of limitations in this study, including those associated with use of a retrospective design. However, we believe that the use of a large data set over a 10-year period adds strength to the findings, suggesting that the trends identified are not by chance. The data reported here are limited to patients who sought help from a poison center and may not reflect the full population of patients with therapeutic errors involving insulin in the ambulatory care setting. Our study focused on patients with an unintentional therapeutic error involving insulin and may not reflect all adverse events involving insulin. Further research in this area may be warranted.

In summary, we report a consistent and increasing trend over a 10-year period of insulin-related unintentional therapeutic errors in the ambulatory setting. These unintentional therapeutic errors occur more commonly in the evening, in adults >40 years, and in females. With their constant availability, poison centers appear to be an increasingly important resource for patients with an adverse event involving insulin.

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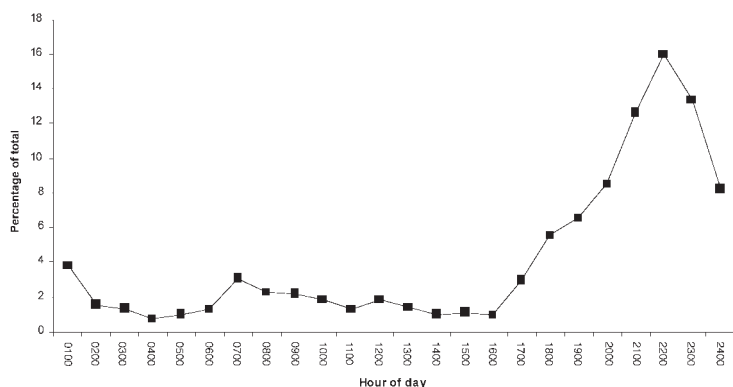
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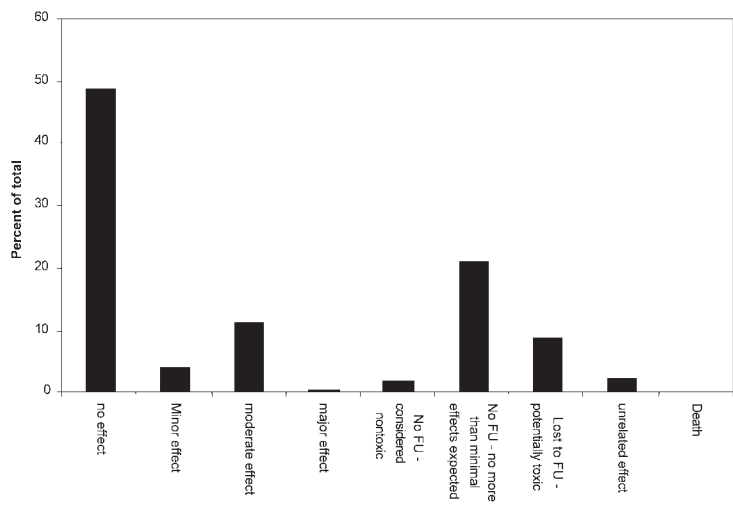
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**Conflict of interest:** Authors reported none



**Figure 5.** Time of day of unintentional therapeutic errors involving insulin.



**Figure 6.** Medical outcome of unintentional therapeutic errors involving insulin. FU = follow-up.

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Errores Terapéuticos no Intencionales Relacionados con Insulina en el Escenario Ambulatorio Reportados a Centros de Envenenamiento

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EXTRACTO

**TRASFONDO:** Los eventos adversos con drogas en el escenario de cuidado ambulatorio no son inusuales y pueden causar morbilidad significativa. Existe poca investigación sobre el manejo de eventos adversos con drogas relacionados con insulina en el escenario de pacientes ambulatorios.

**OBJETIVO:** El presente estudio analiza pacientes con errores terapéuticos no intencionales relacionados con insulina manejados por 9 centros de control de envenenamiento regionales.

**MÉTODOS:** Se llevó a cabo una búsqueda retrospectiva de todos los expedientes relacionados con insulina en 9 centros de envenenamiento, que cubrían la población de 4 estados para los años 2000 al 2009. Un subgrupo de la población de estudio fue seleccionado con una razón para la exposición a un "error terapéutico no intencional".

**RESULTADOS:** Hubo 3,819 exposiciones con insulina reportadas, con un aumento en la incidencia anual de exposiciones con insulina de 279% (de 170 pacientes/año a 645 pacientes/año) y un aumento anual promedio de 18%. Los errores terapéuticos no intencionales con insulina ocurrieron principalmente en adultos >40 años (73%), 63% de éstos féminas. Hubo un aumento pronunciado en las horas más tardías de la noche, con 71% entre 1800 y medianoche y las 2200 como hora pico. La mayoría (n = 1803, 70%) de los pacientes fueron atendidos en una localidad que no era una instalación de cuidado de salud, principalmente en su propia residencia.

**CONCLUSIONES:** Este es el primer reporte de una tendencia creciente de errores terapéuticos no intencionales relacionados con insulina en el escenario ambulatorio. Nuestro estudio destaca un número de notables características que incluyen: 1) un aumento consistente y dramático en los errores terapéuticos no intencionales relacionados con insulina a lo largo del periodo de 10 años, 2) una incidencia alta de errores terapéuticos no intencionales relacionados con insulina en las horas más tardías de la noche, y 3) una incidencia alta de errores terapéuticos no intencionales relacionados con insulina que involucran adultos >40 años y féminas. Con su disponibilidad 24/7, los centros de envenenamiento parecen ser un recurso de importancia creciente para pacientes con un error terapéutico no intencional relacionado con insulina.

Traducido por Ana E Vélez

Erreurs Accidentelles Rapportées aux Centres Antipoison Impliquant l'Insuline

HA Spiller, DJ Borys, ML Ryan, TS Sawyer, et BL Wilson

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RÉSUMÉ

**OBJECTIF:** Analyser dans les 9 centres antipoison, les dossiers des patients qui ont eu des erreurs accidentelles impliquant l'insuline.

**MÉTHODES:** Une étude rétrospective a été effectuée en incluant tous les dossiers impliquant l'insuline dans 9 centres antipoison chez la population de 4 états américains pour les années 2000 à 2009. Un sous groupe de la population étudiée a été sélectionné pour exposition accidentelle ou erreur thérapeutique.

**RÉSULTATS:** Un nombre de 3,819 expositions à l'insuline a été rapporté, avec une augmentation de l'incidence annuelle de 279% (de 170 patients/année à 645 patients/année). Les erreurs accidentelles impliquant l'insuline ont été observées principalement chez les patients de plus de 40 ans (73%), et 63% étant des femmes. Il y avait une augmentation importante en début de soirée, avec 71% des erreurs survenant entre 1800 et minuit avec un pic à 2200. Les patients (n = 1803, 70%) étaient traités principalement à la maison et non dans des centres hospitaliers.

**CONCLUSIONS:** Il s'agit d'un premier rapport décrivant les erreurs accidentelles avec l'insuline dans un milieu ambulatorio. Cette étude a mis en évidence les facteurs suivants: une augmentation des erreurs accidentelles à l'insuline au cours des 10 dernières années; une incidence élevée d'erreurs en début de soirée et impliquant les personnes de plus de 40 ans et principalement les femmes. Étant ouvert 24/7, les centres antipoison semblent être une ressource importante pour les patients qui présentent des erreurs accidentelles à l'insuline.

Traduit par Louise Mallet