

lets, $218 \times 10^9/L$; C-reactive protein, 5 mg/L; fibrin, 3.10 g/L; serum creatinine, 93 $\mu\text{mol/L}$; and serum lactate dehydrogenase, 329 IU/L (reference range, 219–439 IU/L). A serum immunofixation was performed and revealed a monoclonal IgM κ (2 g/L). Bone radiography revealed a right tibial condensation. A bone marrow biopsy specimen did not reveal any abnormal lymphoid infiltrate and was otherwise normal. The results of serologic tests for hepatitis C virus, hepatitis B virus, and human immunodeficiency virus were negative. Serum ferritin level was 140 $\mu\text{g/L}$. The serum C3 level was 1.26 g/L (reference range, 0.75–1.5 g/L), the serum C4 level was 0.16 g/L (reference range, 0.16–0.38 g/L), and the total complement UH 50% level was 93 (reference range, 60–80). The search for serum antinuclear antibody, rheumatoid factor, and cryoglobulin was negative as was the direct Coombs test result.

Schnitzler syndrome was diagnosed according to previously published criteria.¹ Treatment with a combination of 2 antihistamines was started without significant improvement. In July 2004, addition of 5 mg of prednisone led to a partial symptom improvement. Prednisone was progressively tapered then stopped in June 2006 with persistence of arthralgias, bone pain, and episodic urticaria. In September 2006, the patient received intermittent aspirin or non-steroidal anti-inflammatory drugs, and serum immunofixation showed the switch from monoclonal IgM κ to IgG κ (confirmed in March 2007) associated with few persistent symptoms. All the symptoms progressively cleared with the concomitant disappearance of any monoclonal component from January 2008 to date.

This is the first report, to our knowledge, of the spontaneous, persistent remission of the syndrome, concomitant to the disappearance of the monoclonal gammopathy. Another case of spontaneous remission was recently reported but with the persistence of the monoclonal gammopathy and episodic cold- or stress-induced crisis.⁴ Although not formally demonstrated, a causal link between Schnitzler syndrome and the IL-1 pathway is reinforced by the notable effect of the synthetic IL-1 receptor antagonist anakinra or by treatment regulating IL-1, such as pefloxacin.⁵ Anakinra is effective on nearly all symptoms and in all patients.⁶ Furthermore, recent data suggested that a dysfunction of the inflammasome, a multiprotein complex that regulates IL-1 secretion, may play a pivotal role in the physiopathology of the disease.⁷ Although our data do not allow formally ruling out a concurrent development due to a common causal agent, our case report is more likely to support a causal relationship between the monoclonal gammopathy and the occurrence of the syndrome, which may be due to either the IgM by itself, for instance, because of a specific autoantibody activity, or mediators produced by the clonal cells or their environment. Precise mechanisms of the interaction of any of these clonal cell products with the IL-1 pathway remain to be determined.

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EPINEPHRINE AUTOINJECTOR DELIVERY SYSTEMS: AN INVESTIGATION OF USABILITY AND PREFERENCE

Guerlain et al^{1,2} recently provided results of 2 human factor analyses comparing Intelliject's epinephrine autoinjectors with EpiPen and Twinject. We would like to point out several flaws in these 2 studies that limit the interpretation of their findings.

The first study¹ compared Intelliject's 2 prototypes (INT01 and INT02) with EpiPen and Twinject for usability and preference. In this study, the first major confounder was the inclusion of participants who had prior experience with epinephrine autoinjectors. The comparisons were biased because half the participants in each age group had seen, used, or been trained on how to use EpiPen or Twinject but were unfamiliar with the Intelliject autoinjectors. Excluding participants with autoinjector experience would have controlled for these factors. Second, the preferred prototype that included voice prompting instructions (INT02, described as being independent of the injection mechanism) was found to have malfunctions that would require design changes. We would be interested to know the answers to the following questions: What is the reliability of the voice functionality? Will it work when it is needed? What is the potential for the visual signals and voice prompting to entice curious children? Third, it is not clear why the authors selected a within-participant protocol for comparing the 4 autoinjectors because learning bias is inevitable in such protocols. Response to the stressor stimuli is weakened with each subsequent device that is tested, thereby biasing the comparisons. A between-participant strategy (eg, 5–8 participants per device) could have controlled for these factors and may have improved the potential for the stimulus to be a useful stressor. It would be interesting to know whether the stressor stimuli used in this study has been empirically tested and whether it is a valid representation of the level of stress experienced by patients with anaphylaxis and their caregivers.

The second study investigated Intelliject's novel epinephrine autoinjector (NEA) for its sharps injury prevention, validation, and comparable analysis with EpiPen and Twinject.² We identified several problems within this study as well. First, the validation of the sharps injury features of NEA was tested on practicing nurses, who were presumably selected to test the autoinjector because of their expertise in evaluating unintentional needle exposure. However, an important goal of usability testing approaches is to evaluate the system on the intended end users of the autoinjectors (ie, participants

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who are representative of the target user population) and to obtain continual input and feedback from these end users throughout the development cycle of the device being tested.^{3,4} Second, because an orange was used as the injection test site, the interactive feature (ie, voice instructions) was disabled to avoid the provision of conflicting instructions to the participant (ie, to inject the device into the thigh). Hence, this may have diminished the purpose of usability evaluation—to reveal errors and problems with the device, particularly for this distinguishing feature, which is not available in other autoinjectors. Third, this study also used a within-participants protocol, where each of the 28 participants tested the NEA 18 times in a row, likely increasing their familiarity with the new device (learning bias). This is particularly problematic because participants were subsequently asked to compare the NEA with EpiPen and Twinject (for which practice opportunities were not provided). Thus, repetitive testing with NEA likely predisposed participants to prefer the new device. Furthermore, preferences were based on recall of personal experiences (whether participants knew of someone who had used an epinephrine autoinjector incorrectly) rather than on empirical findings. These methods likely resulted in biased comparisons (recall bias) and are also not a valid indication of safety or usability. Fourth, the primary objective of the study was to visually observe “needle injection success” (ie, whether the needle injected or retracted by checking for puncture in the paper placed on the orange). However, the authors claim that the NEA needle resides in the patient for less time than the other 2 products (EpiPen and Twinject) and thus may lessen the potential for injection site reactions (ie, pain, bruising, or bleeding). This statement is indefensible because the study did not perform a head-to-head comparison with existing autoinjectors to warrant this claim.

Finally, it is important to iterate that neither of the analyses^{1,2} evaluated the current EpiPen design (which has a needle protection device that extends and locks into place once the dose is administered) or addressed the cost of the different devices, particularly for the voice-activated model. We also question the interpretation of findings because both studies appear to have conflict of interest: investigator salaries were funded by Intelliject in the first study,¹ whereas the same funder assisted with the preparation of the manuscript in the second study.²

On the basis of the possible flaws outlined in these 2 articles,^{1,2} we believe that further studies with rigorously designed head-to-head comparisons are needed before drawing any conclusions.

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IMMEDIATE ALLERGIC REACTIONS TO B-LACTAMS: DIAGNOSTIC ACCURACY OF SKIN TESTS

β -Lactam antibiotics are the most frequent cause of drug allergic reactions. During the last few decades, changes in prescribing habits have caused amoxicillin and amoxicillin-clavulanic to replace benzylpenicillin as the most frequently involved agents.¹ Skin tests with major (penicilloyl-polylysine [PPL]) and minor (minor determinant mixture [MDM]) penicillin determinants are considered the first diagnostic procedure in the assessment of immediate allergic reactions.^{2,3} However, in the last few years several authors have described a decrease in the diagnostic sensitivity of these determinants.¹ This could be because a significant proportion of patients produce specific and selective antibodies against the side chain of amoxicillin or other β -lactam antibiotics.¹ There is some controversy about what determinants should be included in the evaluation of an allergic reaction to β -lactam.³⁻⁵

We have evaluated the outcomes of skin tests with different β -lactam determinants. In addition, we have assessed whether skin testing patterns are different in patients with reactions to benzylpenicillin than in patients with reactions to aminopenicillins.

Between April 1995 and June 2009, we included all patients who consulted our Allergy Unit because of a clinical history of an immediate allergic reaction (anaphylaxis or urticaria) to benzylpenicillin or aminopenicillins. The study was approved by the ethics committee of the hospital, and informed written consent was obtained from all patients. To compare the results, the sample was divided into 2 groups: patients who had had a reaction to benzylpenicillin (group A) and patients who had had a reaction to aminopenicillins (group B).

A detailed clinical history was obtained from all the patients. Skin tests were performed as previously described,³ with PPL (10^{-5} M) and MDM (10^{-2} M) (Allergopen, Allergopharma, JGKG, Reinbek, Germany, until 2006 and afterward from Diater, Madrid, Spain), benzylpenicillin (10,000 IU), and amoxicillin (20 mg/mL). Initially, skin prick tests were performed. A wheal larger than 3 mm with erythema was considered a positive result. If the skin prick test result were negative, intradermal tests were performed. A 3-mm change in the diameter of the initial wheal associated with flare was considered positive. A positive result to one or more determinants was considered diagnostic. When skin test results were negative, a drug provocation test with the suspected β -lactam was performed under strict hospital surveillance.

Specific IgE to benzylpenicillin and amoxicillin was performed with the CAP-FEIA System (Phadia, Uppsala, Sweden). The positive cutoff value was 0.35 kUA/L or higher.

One thousand thirty-one patients with a suspected immediate hypersensitivity reaction to BP or aminopenicillins were evaluated. Of them, 281 patients (27.2%) had a positive result in the study. Two hundred sixty-four patients (94%) had positive skin test results, and 16 patients (5.7%) had a positive challenge test result. Only 1

Disclosures: Dr Moreno has participated in a trial to validate a diagnostic product to β -lactam allergy (DAP-REF CEIC:08/731) from Diater Company, although the research in this paper is not related in any way to compensation received from this company. All other authors do not have any conflict of interest.

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