Stability Over Time of In-Hospital–Compounded Amoxicillin Capsules and Ceftriaxone Patch Tests for Drug Allergy Testing

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Drug hypersensitivity reactions account for 15% of adverse drug reactions [1]. For both immediate and nonimmediate reactions, re-exposure to the culprit drug through skin testing and/or oral drug challenge is part of the diagnostic process. Since patch test batteries do not include all the drugs involved in hypersensitivity reactions and no commercial drug provocation tests are available to date, compounding is often necessary prior to the exploration of drug hypersensitivity reactions [2]. Compounding raises 2 major issues, especially in the setting of specialized allergy centers. First, it is time-consuming, the tests being manufactured mainly for a single patient and kept no more than 1 day. Second, compounded drugs may undergo chemical degradation between compounding and use, either in liquid, semiliquid, or solid forms [3], leading, at least in theory, to false-negative results if the incriminated drug is degraded into inactive metabolite(s) or, in contrast, to false-positive results if degradation products are irritants or themselves act as allergens. Manufacturing batches of standardized tests that can be stored prior to use and with an expiry date based on stability studies would therefore appear to be a valuable solution for fulfilling needs not met by pharmaceutical companies for the exploration of drug hypersensitivity reactions.

In this pilot study, we investigated the physicochemical stability of drug provocation tests with amoxicillin and patch tests with ceftriaxone in water (aq) and petrolatum (pet), since ß-lactams are the antibiotics most frequently reported to cause hypersensitivity reactions [4].

To compound amoxicillin capsules, available capsules of amoxicillin (Clamoxyl 500 mg) were opened, and the powder contents were ground with colloidal silica and carmine powder in a mortar. The mixed powder was then distributed in gelatin hard capsules using a manual capsule filling machine. Three different batches of amoxicillin hard capsules were packaged in individual bags away from light. Studies were conducted for 12 months at room temperature (ie, 15-25°C). At each predetermined time point, 3 hard capsules from each batch were opened and sampled for subsequent visual examination and quantification of amoxicillin. Ceftriaxone patch tests were compounded by diluting ceftriaxone powder (ceftriaxone 1g Mylan, powder for solution for injection) in water to reach 0.1 g/mL or mixing it with petrolatum to reach 0.1 g/g. Ceftriaxone 10% aq or pet was then distributed in 3-mL syringes. Three batches of syringes containing ceftriaxone 10% aq or pet were stored at –20°C for 90 days in individual bags away from light. At each predetermined time point, 3 syringes for each batch and each condition (pet and aq) were thawed: 1 for immediate analysis and 2 for a further 48 hours' storage before analysis, the first at 25°C and the second at 4°C. Analyses included visual examination and quantification of ceftriaxone (see Supplementary material for extended Material and Methods).

Protocols for graded oral challenge with amoxicillin require oral administration of increased doses, eg, ranging from 5 mg (1:100) to 250 mg (1:2) until the full dose is reached (ie, 500 mg, which is commercially available) [5]. We therefore compounded 5-mg and 250-mg hard capsules for further study. Amoxicillin content quantified using high-performance liquid chromatography with tandem mass spectrometry (HPLC-MS/MS) remained above 90% of the expected quantity in hard capsules of both dosages after a 12-month storage period at room temperature (Figure, A). We did not observe any change in the appearance of the intact capsules or of the powder between day 0 and month 12 (Supplementary Figure 1A).

Ceftriaxone was compounded at 10% aq or pet for patch testing in 3-mL syringes to be applied on the skin and occluded [6]. Ceftriaxone, which was quantified using HPLC-MS/MS, remained above 90% of the expected quantity, both in petrolatum and in water (Figure, B). Furthermore, we did not detect any changes in visual appearance throughout the study (Supplementary Figure 1B)

To the best of our knowledge, this is the first report of the long-term stability of ß-lactam tests compounded to fulfill a need that remains unmet by pharmaceutical companies. In our institution, manufacturing is carried out in the pharmacy department to remove this time-consuming activity from nurses and to guarantee a quality close to industrial guidelines (ie, Good Manufacturing Practice). We compounded capsules from commercial 500-mg amoxicillin doses, since no bulk forms were available. It was then necessary to add a diluent excipient to the formulation to fill the capsules, thus making it possible to compound large series of capsules at once. For this purpose, we decided to use colloidal silica, which is very common in oral and topical pharmaceutical products and is generally considered nontoxic and nonirritant [7]. Similarly, we compounded patch tests in water or petrolatum containing a 10% commercial form of ceftriaxone in the absence of a bulk form. However, the lyophilized ceftriaxone we used could be considered a pure substance, since a vial contains 1193 mg

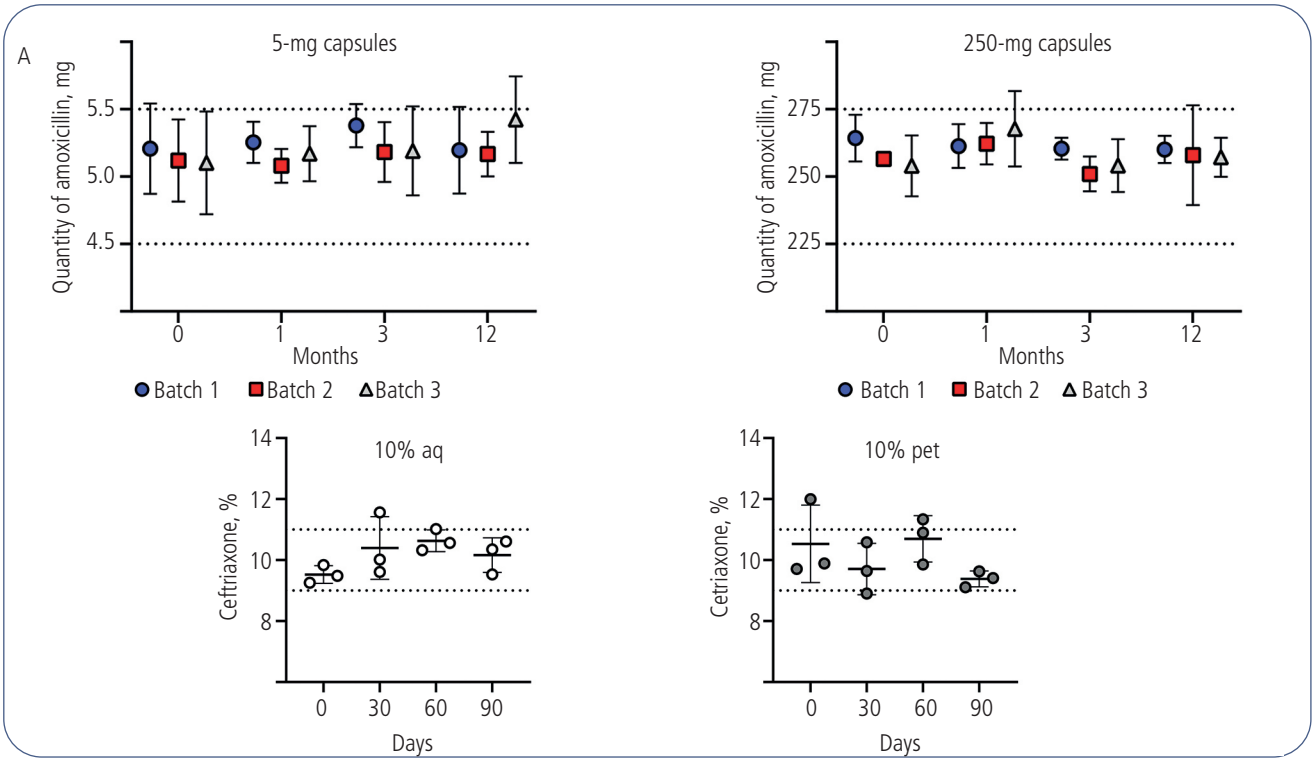

Figure. A, Stability of 5-mg and 250-mg amoxicillin hard capsules for graded oral challenge. B, Stability of ceftriaxone in water and petrolatum for patch testing.
Horizontal lines and error bars: mean (SD). Dotted lines: 10% interval from the theoretical quantity.

of sodium ceftriaxone, ie, 1000 mg of pure ceftriaxone, with no additional excipient other than sodium. This is in line with current guidelines, which recommend diluting the drug at 5% to 10% aq or pet [8-10]. A literature review highlighted the variable stability of compounded and commercial patch test allergens and found that many degrade when in storage [11]. We decided to store ceftriaxone patch tests at –20°C, since ceftriaxone is particularly susceptible to degradation, which is dependent on temperature and concentration [12,13].

Drug provocation tests with amoxicillin and ceftriaxone patch tests compounded in water and petrolatum were stable, respectively, for 1 year at room temperature and for 90 days when frozen. This study enabled the manufacture of batches, rather than extemporaneous compounding. Our pilot study could constitute a first step toward the development of standardized manufactured tests for exploring drug hypersensitivity.

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Conflicts of Interest

The authors declare that they have no conflicts of interest.

References

1. Demoly P, Adkinson NF, Brockow K, Castells M, Chiriac AM, Greenberger PA, et al. International Consensus on drug allergy. Allergy. 2014;69(4):420-37.
2. Brockow K, Garvey LH, Aberer W, Atanaskovic-Markovic M, Barbaud A, Bilo MB, et al. Skin test concentrations for systemically administered drugs -- an ENDA/EAACI Drug Allergy Interest Group position paper. Allergy. 2013;68(6):702-12.
3. Stella VJ. Chemical drug stability in lipids, modified lipids, and polyethylene oxide-containing formulations. Pharm Res. 2013;30(12):3018-28.
4. Shenoy ES, Macy E, Rowe T, Blumenthal KG. Evaluation and Management of Penicillin Allergy: A Review. JAMA. 2019;321(2):188-99.
5. Audicana MT, Ortega NR. Spanish Society of Allergology and Clinical Immunology (SEAIC) Vision of Drug Provocation Tests: Reply. J Investig Allergol Clin Immunol. 2022;32(3):242-3.
6. Brockow K, Romano A, Blanca M, Ring J, Pichler W, Demoly P. General considerations for skin test procedures in the diagnosis of drug hypersensitivity. Allergy. 2002;57(1):45-51.
7. Sheskey PJ, Hancock BC, Moss GP, Goldfarb DJ. Handbook of Pharmaceutical Excipients. 9th edition. London; Washington: Pharmaceutical Press; American Pharmaceutical Association; 2020.
8. Barbaud A, Gonçalo M, Bruynzeel D, Bircher A, European Society of Contact Dermatitis. Guidelines for performing skin

tests with drugs in the investigation of cutaneous adverse drug reactions. Contact Dermatitis. 2001;45(6):321-8.
9. Romano A, Atanaskovic-Markovic M, Barbaud A, Bircher AJ, Brockow K, Caubet JC, et al. Towards a more precise diagnosis of hypersensitivity to beta-lactams - an EAACI position paper. Allergy. 2020;75(6):1300-15.
10. De Groot AC. Patch Testing. 5th Edition. Wapserveen: acdegroot publishing; 2022.
11. Joy NM, Rice KR, Atwater AR. Stability of patch test allergens. Dermatitis. 2013;24(5):227-36.
12. Cantón E, Esteban MJ, Rius F. Factors affecting the stability of ceftriaxone sodium in solution on storage. Int J Pharm. 1993;92(1):47-53.
13. Herrera-Hidalgo L, López-Cortes LE, Luque-Márquez R, Gálvez-Acebal J, de Alarcón A, López-Cortes LF, et al. Ampicillin and Ceftriaxone Solution Stability at Different Temperatures in Outpatient Parenteral Antimicrobial Therapy. Antimicrob Agents Chemother. 2020;64(7):e00309-20.

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