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Math-free guides for glycerin and allergens at variable subcutaneous injection volumes

How's my dosing? Update

Thomas J. Grier, PhD; Lorie M. Converse, NP-C; Donna J. Rekkerth, MS, FNP; Kevin E. Renahan, MSc

Medical and Scientific Affairs, Stallergenes Greer, Lenoir, North Carolina

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ABSTRACT

Background: Current summaries of effective maintenance dose ranges for subcutaneous immunotherapy (SCIT) are based on administration of 0.5-mL volumes. Extract formulations delivering equivalent dose ranges for practices using different injection volumes have not been reported, and calculation of the final glycerin concentrations in these solutions remains an inconvenient and repetitive process.

Objective: To create math-free guides for allergen doses and glycerin concentrations that identify the extract concentrate volumes required to deliver doses within the ranges cited in the 2011 immunotherapy practice parameters for clinicians using 5.0-mL maintenance vials and injection volumes ranging from 0.2 to 1.0 mL.

Methods: Algebraic calculations were performed to determine the specific combinations of extract concentrate strengths, volumes of these products in patient vaccines, and injection volumes needed for administration of target allergen doses spanning the current SCIT practice parameter recommendations.

Results: For each product or group (nonstandardized extracts), tables were constructed to define the allergen doses provided by various combinations of extract concentrate volumes and injection volumes. The values within the effective dose ranges for each product were highlighted to facilitate comparisons of specific conditions relevant to allergy specialists. Glycerin tables were also created to permit convenient assessments of the final concentrations of this stabilizer in patient prescriptions.

Conclusion: SCIT dosing and glycerin tables are useful tools to assist allergists with practice decisions that involve variable patient formulas and injection volumes and can help identify suitable conditions for treatment of patients presenting with diverse allergen sensitivities and specificity profiles.

Introduction

Subcutaneous administration of allergenic extracts at effective and safe maintenance doses is a fundamental practice in allergy clinics across the United States and worldwide.[1] Identification of optimal dose ranges and treatment regimens for patients with a wide variety of allergen sensitivities can be challenging.[2–6] Qualitative and quantitative differences in natural exposures to provocative allergens can also affect the severity of allergic diseases and resulting tolerances to extracts administered in immunotherapy protocols.[1,7–9]

Allergen doses delivered during subcutaneous immunotherapy (SCIT) are defined by 4 variables: stock extract concentrations, volumes of these solutions added to patient vials, total volumes of patient vial formulations, and injection volumes.[2,6] Formulation of patient-specific allergen vaccines remains a highly individualized process.[1,2] In addition to the targeted allergen levels, patient sensitivity, allergen compatibility, cross-reactivity, and final glycerin or stabilizer concentrations are important considerations when designing and preparing SCIT vaccines.[2,6,10–13]

Probable effective dose ranges for licensed products manufactured in the United States have been reported in recent SCIT practice parameter updates based on injection of 0.5-mL volumes of maintenance-strength formulas.[2,3] However, owing to the diversity and variability of allergen sensitivities observed in clinical settings, it is not uncommon for patient treatments to require extract volumes and maintenance doses different from those cited in the practice parameters. To reduce irritation at the injection site associated with elevated allergen and/or glycerin concentrations in these formulas, some clinicians administer lower volumes (0.2–0.4 mL) of SCIT vaccines, whereas others have opted for higher injection volumes

Reprints: Thomas J. Grier, PhD, Stallergenes Greer, PO Box 800, Lenoir, NC 28645; E-mail: tgrier@greerlabs.com.

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(0.6–1.0 mL) using lower component concentrations, particularly for patients treated with relatively large numbers of extracts from diverse allergen sources (minimal or no cross-reactivity with other native species).[5,6,12]

Preparation of patient-specific mixtures providing extract doses within these target ranges can be accomplished via manual or spreadsheet-based algebraic calculations or math-free dosing guides that circumvent the need for these repetitive mathematical steps.[2,6] These tables help simplify the preparation of maintenance formulations for probable effective dosing ranges based on 0.5-mL injection volumes but do not include guides for alternative injection volumes, final glycerin concentrations, or nonstandardized extracts in protein nitrogen unit (PNU) strengths. The purpose of the present report is to provide clinicians with updated, 1-step conversion tables for glycerin, standardized allergenic extracts, and nonstandardized products in wt/vol and PNU strengths in 5.0-mL maintenance vials administered at injection volumes ranging from 0.2 to 1.0 mL.

Methods

Recommended SCIT Dose Ranges

Effective dose ranges and target concentrations described in the enclosed tables were consistent with those cited in the 2011 SCIT practice parameter update for allergenic extracts in maintenance-strength patient vaccines.[2] Estimates for nonstandardized products labeled in PNU not included in prior practice parameter summaries were determined using mean values of licensed extracts from one manufacturer (Stallergenes Greer, Lenoir, North Carolina). Short ragweed doses were calculated using extract concentrates at 200 Amb a 1 (antigen E or AgE) U/mL, a value typical of many 1:20 wt/vol glycerinated product lots manufactured at Stallergenes Greer and other licensed US allergen manufacturers.[6]

Extract Volume Computations

SCIT practice parameter recommendations are based on 0.5-mL injection volumes that contain defined ranges of nonstandardized extracts (labeled in wt/vol) and/or standardized extracts (labeled in potency units per milliliter). For clinics that use alternative injection volumes for their maintenance-strength formulations, proportional adjustments in the volumes of extract concentrates are required to produce equivalent or revised doses during SCIT regimens. In this report, these values were determined for 5-mL patient vials and specific combinations of extract concentrate volumes (0.05–5.0 mL) and injection volumes (0.2–1.0 mL) using mass conservation and dilution factor derivations.[6] For example, injection of a 2,000–bioequivalent allergy units (BAU) maintenance dose of cat extract in a 0.5-mL volume requires preparation of a 4,000-BAU/mL formula (2,000 BAU per 0.5 mL). The volume of 10,000 BAU/mL of cat extract needed to prepare a 5-mL formula at 4,000 BAU/mL becomes $(V_1)(10{,}000) = (5.0)(4{,}000)$ or $V_1 = 2.0$ mL. Using the dilution factor method with the same example, the ratio of extract concentrate strength to target concentration was first determined (10,000/4,000 = 2.5), then the total volume of the maintenance vaccine was divided by this factor to yield the concentrate volume needed (5.0 mL/2.5-fold dilution = 2.0 mL).

SCIT Dose Tables at Variable Injection Volumes

With the use of the algebraic methods described above, allergen dose tables were created for standardized (cat, dust mite, short ragweed, pasture grasses, Bermuda grass) and nonstandardized products frequently included in SCIT protocols. For each product and table, extract concentrate volumes were selected to yield doses that spanned the probable effective ranges, with the current practice parameter recommendations highlighted for convenient comparisons with alternative treatment conditions.

Glycerin Calculator

A glycerin table was also created to circumvent the multiple, repetitive steps required to calculate the final glycerin concentrations of customized SCIT vaccine formulations. The glycerin levels in 5-mL patient vials were determined by combining the individual contributions from glycerin-free components (aqueous extract concentrates, normal saline diluent, human albumin-saline diluent, buffered saline diluent) with those that contained 10% glycerin (10% glycerin-saline diluent) and 50% glycerin (glycerinated extract concentrates, 50% glycerin-saline diluents). As with the dose tables, the glycerin levels in SCIT vaccines at final volumes other than 5 mL can be adapted from these data.

Human participation was not required to perform these extract dose calculations; thus, this study was exempt from review by an institutional board or human subjects protection committee.

Results

SCIT Practice Parameter Dose Recommendations

The extract concentrations required to deliver probable effective allergen doses in different SCIT injection volumes are summarized in Table 1. Target levels are given for the 0.5-mL injections specified in recent SCIT practice parameter updates, as well as those at lower

Table 1
Probable Effective Subcutaneous Immunotherapy Maintenance Doses and Target Concentrations for Standardized and Nonstandardized Extracts at Variable Injection Volumes

Extract	Probable Effective Dose Ranges and Target Extract Concentrations at Variable Injection Volumes			
	Dose Range	Target Concentration by Injection Volumes		
		0.2 mL	0.5 mL	1.0 mL
Short ragweed,[a] AgE U or μg of Amb a 1	6–12	30–60/mL	12–24/mL	6–12/mL
Cat, BAU	1,000–4,000	5,000–20,000/mL	2,000–8,000/mL	1,000–4,000/mL
Dust mites,[b] AU	500–2,000	2,500–10,000/mL	1,000–4,000/mL	500–2,000/mL
Pasture grasses,[c] BAU	1,000–4,000	5,000–20,000/mL	2,000–8,000/mL	1,000–4,000/mL
Bermuda grass, BAU	300–1,500	1,500–7,500/mL	600–3,000/mL	300–1,500/mL
Pollen, wt/vol	1:100–1:200	1:40–1:80 wt/vol	1:100–1:200 wt/vol	1:200–1:400 wt/vol
Fungi, wt/vol	HTD	1:40–1:80 wt/vol	1:100–1:200 wt/vol	1:200–1:400 wt/vol
Insects, wt/vol	HTD	1:40–1:80 wt/vol	1:100–1:200 wt/vol	1:200–1:400 wt/vol
Animals, wt/vol	HTD	1:40–1:80 wt/vol	1:100–1:200 wt/vol	1:200–1:400 wt/vol
Dog epithelia, wt/vol	HTD	1:40–1:80 wt/vol	1:100–1:200 wt/vol	1:200–1:400 wt/vol
Dog AP, μg of Can f 1	15 μg	75 μg/mL	30 μg/mL	15 μg/mL

Abbreviations: AgE, antigen E or Amb a 1; BAU, bioequivalent allergy unit; AU, allergy unit; wt/vol, weight-to-volume ratio; HTD, highest tolerated dose.
[a]Short ragweed extracts standardized based on AgE concentrations. 1 unit equals 1 μg.
[b]*Dermatophagoides pteronyssinus* or *Dermatophagoides farinae*.
[c]Kentucky blue/June, meadow fescue, orchard, perennial rye, redtop, sweet vernal, and Timothy grasses.