

Determination of nonirritating concentrations of antibiotics for intradermal skin tests in Korean adults



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Clinical Implications

- Although the data of skin test with drugs are still scarce, a positive result at nonirritating concentrations is generally accepted for the diagnosis of drug allergy. We investigated nonirritating concentrations for intradermal skin test with antibiotics.

TO THE EDITOR:

Antibiotics are essential therapeutics used to treat various infections.¹ However, immediate hypersensitivity reactions to antibiotics, ranging from mild urticaria to fatal anaphylaxis that occur within 1 to 2 hours after drug exposure, can force physicians to prescribe less effective alternative treatments.² Although the diagnostic capabilities of skin tests with antibiotics except for penicillin have not been validated, skin tests are the most common tool used worldwide to identify drugs that cause immediate hypersensitivity reactions.³ In this study, we intended to evaluate the maximal nonirritating concentrations (NICs) of antibiotics used in intradermal skin tests (IDTs) in Korean adults.

We enrolled 49 volunteers who were 18 years old or older with no history of drug hypersensitivity. This study was approved by the Institutional Review Board at SMG-SNU Boramae Medical Center (Institutional Review Board no. 16-2013-131). The maximal NICs of the following 17 common antibiotics were investigated: ceftazidime, ceftriaxone, ciprofloxacin, meropenem, vancomycin (CJ HealthCare, Seoul, Korea), ampicillin/sulbactam (Pfizer, Seoul, Korea), azithromycin (Pfizer), aztreonam (Friend Pharm, Seoul, Korea), cefazolin (Yuhan, Seoul, Korea), cefotetan (Jeil Pharmaceutical Co., Seoul, Korea), cefuroxime (Shin Poong Pharm Co., Seoul, Korea), clindamycin (Samjin Pharm, Seoul, Korea), levofloxacin (Ildong Pharmaceutical, Seoul, Korea), nafcillin (Boryung Co., Seoul, Korea), penicillin G (Hanall Biopharma, Seoul, Korea), piperacillin/tazobactam (Chong Kun Dang Pharm Co., Seoul, Korea), and sulfamethoxazole/trimethoprim (Jaytech Biogen, Seoul, Korea). We diluted each drug by using either sterile water or normal saline. Approximately 0.02 to 0.05 mL was injected intradermally into the extensor surface of the forearm to produce a wheal of about 3 mm in diameter. Wheals were measured 15 minutes after the injection. Wheals that increased by 3 × 3 mm in diameter compared with baseline were considered a positive irritant skin response. A negative control was either the normal saline or the

sterile water that was used to dilute the drug. A histamine prick was used as positive control to prove skin reactivity. The *starting concentration* was defined as a concentration 10 times greater than the reference NIC, which was determined in a previous study.⁴ Table 1 lists the reference NIC, the starting concentration, and the NIC from this study. Maximal NICs were investigated as follows: (1) IDTs were performed using the starting concentration to the randomly selected first volunteer. The NIC was then evaluated for 19 more subjects by conducting an IDT with the NIC from the first volunteer. When the first volunteer showed positive result to the starting concentration, IDTs using sequentially (10^{-1} , 10^{-2} , 10^{-3} , and 10^{-4}) diluted drug were performed to the same volunteer until the result was negative (Figure 1; see Figure E1 in this article's Online Repository at www.jaci-inpractice.org). The *initial NIC* was defined as the highest concentration of antibiotics that produced negative result in the first volunteer. The initial NIC from the first volunteer was repeated in 19 more subjects.² If the initial NIC produced positive result in 1 of the 19 subjects, the antibiotics were further diluted and were tested to the same subject until the result was negative (second NIC). The rest of the subjects were tested with the second NIC. Repeated in this way, the concentration that produced negative result in the 20th subject was determined as the maximal NIC. The established maximal NICs for each antibiotic from this study were compared with NICs from a previously published study.⁴

The maximal NICs for antibiotics were as follows: ampicillin/sulbactam (25/12.5 mg/mL), aztreonam (2 mg/mL), ciprofloxacin (0.002 mg/mL), clindamycin (15 mg/mL), nafcillin (0.025 mg/mL), and penicillin G (10,000 U/mL). These NICs were in accordance with previously published NICs (see Table 1). Five cephalosporins (cefazolin, cefotetan, ceftazidime, ceftriaxone, and cefuroxime) were tested in this study. The maximal NICs for cefazolin, ceftazidime, cefuroxime, and ceftriaxone were similar to concentrations of cephalosporins typically used for skin tests.⁵ However, the NICs of cefotetan (0.002 mg/mL) in this study were much lower than those reported in other studies. Two fluoroquinolones were tested in our study; the NIC of ciprofloxacin was comparable to concentrations commonly used (1/1000).⁶ However, that of levofloxacin was 10 times more diluted in this study compared with that used in other studies. The differences in the NICs of cefotetan, azithromycin, and vancomycin among the volunteers were greater than 100-fold. The NICs for cefotetan for each volunteer ranged from 0.002 to 20 mg/mL, for azithromycin from 0.0001 to 0.1 mg/mL, and for vancomycin from 0.00005 to 0.05 mg/mL.

In this study, we evaluated the maximal NICs for 17 antibiotics commonly prescribed to Korean adults. Our study tested several NICs in accordance with previously reported concentrations. The maximal NICs of ampicillin/sulbactam, aztreonam, ciprofloxacin, clindamycin, nafcillin, and penicillin G determined in this study were similar to the reference NICs. Alternatively, for azithromycin, levofloxacin, meropenem, piperacillin/tazobactam, sulfamethoxazole/trimethoprim, and vancomycin, we observed a discrepancy between the reference concentrations and the NIC from this study (≥ 10 -fold). Only a small amount of literature has addressed

TABLE 1. Nonirritating concentrations for 17 commonly used antibiotics

Antibiotics	Reference NIC*	Starting concentration†	Maximal NIC‡
Ampicillin/sulbactam	25/12.5	250/125	25/12.5
Azithromycin§	0.01	0.1	0.0001
Aztreonam	2	20	2
Cefazolin	33	330	3
Cefotetan§	2	20	0.002
Ceftazidime	10	100	1
Ceftriaxone	10	100	10
Cefuroxime	10	100	1
Ciprofloxacin	0.002	0.02	0.002
Clindamycin	15	150	15
Levofloxacin	0.005	0.05	0.0005
Meropenem	1	10	0.1
Nafcillin	0.025	0.25	0.025
Penicillin G	10,000 U/mL	100,000 U/mL	10,000 U/mL
Piperacillin/tazobactam	4.5	45	45
SMT/TMT	0.8/0.04	8/0.4	0.08/0.004
Vancomycin§	0.005	0.05	0.00005

SMT/TMT, Sulfamethoxazole/trimethoprim.

Values are mg/mL except where indicated.

*Reference NICs were those determined in a previous study.⁴

†Starting concentrations were the 10-fold higher concentration than reference NIC.

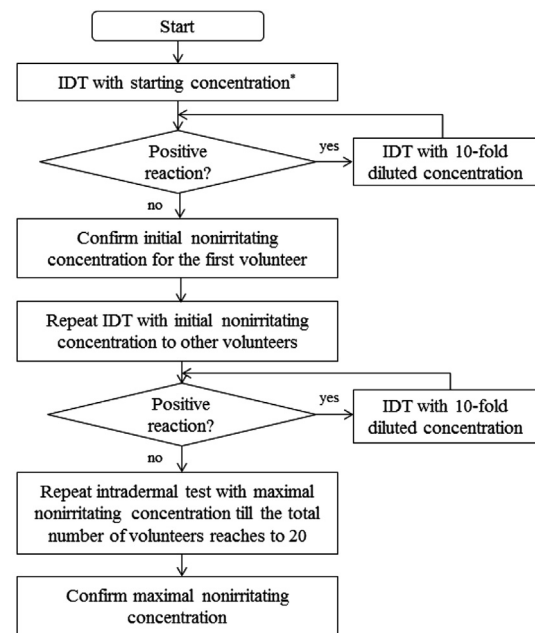
‡Maximal NICs were the NICs established from this study.

§The NICs of azithromycin, cefotetan, and vancomycin were variable among the subjects and we provided the most dilute NICs for these drugs. The number of patients tested per antibiotic was 20.

the NICs of specific antibiotics using normal subjects, and the NICs suggested in each article varied from one another^{1,4,7} (see Table E1 in this article's Online Repository at www.jaci-inpractice.org). Moreover, the NICs from those reports were not validated in Asian populations. Barbaud et al⁸ reported different skin reactivity responses to several chemicals among various ethnicities. With respect to skin reactivity, Asian populations may be more sensitive than whites.⁹ We did observe variability among skin test results in different individuals with cefotetan, azithromycin, and vancomycin, with more than 100-fold differences. In light of our findings, we suggest that the results from IDTs using these particular antibiotics be interpreted with caution.

Five cephalosporins with different chemical structures had discordance. Typically, an NIC of 2 to 3 mg/mL is recommended for IDTs with all cephalosporins.⁵ In this study, all cephalosporins, except ceftriaxone, differed from the reference NIC. Thus, using a standard cephalosporin concentration of 2 to 3 mg/mL during IDTs should be reconsidered.

This study has some limitations. First, the mean age of subjects was younger than those in previously published studies. Skassa-Brociek et al¹⁰ reported that skin reactivity to histamine decreases with age. However, in terms of estimating generally acceptable NICs, it would be more advantageous to test individuals with more reactive skin. Second, although we attempted to follow the concentrations suggested by the European Academy of Allergy and Clinical Immunology and the European Network on Drug Allergy, the number of subjects used to determine the previous NIC for each antibiotic was relatively small.^{1,4,8} There was also a possibility that there were



*Ten times concentrated from suggested maximal nonirritating concentration from previous studies.

FIGURE 1. Determining nonirritating concentrations for 17 commonly used antibiotics. When the first volunteer showed a positive result to the starting concentration, IDTs using sequentially (10^{-1} , 10^{-2} , 10^{-3} , and 10^{-4}) diluted drug were performed to the same volunteer until the result was negative (the initial NIC). The next subject was then tested with the initial NIC. If the second volunteer showed a positive reaction to the initial NIC, further dilution of the study drug was done until the second volunteer showed a negative result (second NIC). The third volunteer was tested from the second NIC and so on until the last volunteer had a negative test result.

subjects in our sample who were already sensitized to the drug tested in spite of a negative clinical history. However, there were subjects among the 19 subjects (other than the first volunteer) who showed positive responses to the initial NICs for each drug. Thus, we thought that it would be very unlikely that the first volunteer was actually sensitized to a specific drug. Third, there is a possibility that different kinds or amounts of excipients in a given drug preparation made the NIC different from the reference NIC. However, Korean government guidelines determine the amount and kinds of excipients so as to minimize the differences of the products from those of other countries such as the United States, Europe, and Japan (International Pharmaceutical Excipients Council). Thus, we believe that there would be no meaningful differences in carriers or excipients. In conclusion, we evaluated the NICs of 17 antibiotics commonly prescribed to Koreans for IDTs. Although we believe that these results should be clinically useful in our populations, additional work will be needed to standardize antibiotics for IDTs in Asian and other populations.

Acknowledgments

We thank the pharmaceutical companies who kindly provided their products for this study. Friend Pharm provided

aztreonam, Jaytech Biogen provided sulfamethoxazole/trime-thoprim, Pfizer Korea provided ampicillin/sulbactam and azi-thromycin, Boryung provided nafcillin, and Hanall Biopharma provided penicillin G.

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This study was supported by a grant of the Korea Healthcare Technology R&D Project, Ministry for Health, Welfare, Republic of Korea (grant no. A092076).

Conflicts of interest: The authors declare that they have no relevant conflicts of interest.

Received for publication July 14, 2016; revised September 14, 2016; accepted for publication September 19, 2016.

Available online November 9, 2016.

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2213-2198

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<http://dx.doi.org/10.1016/j.jaip.2016.09.026>

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APPENDIX

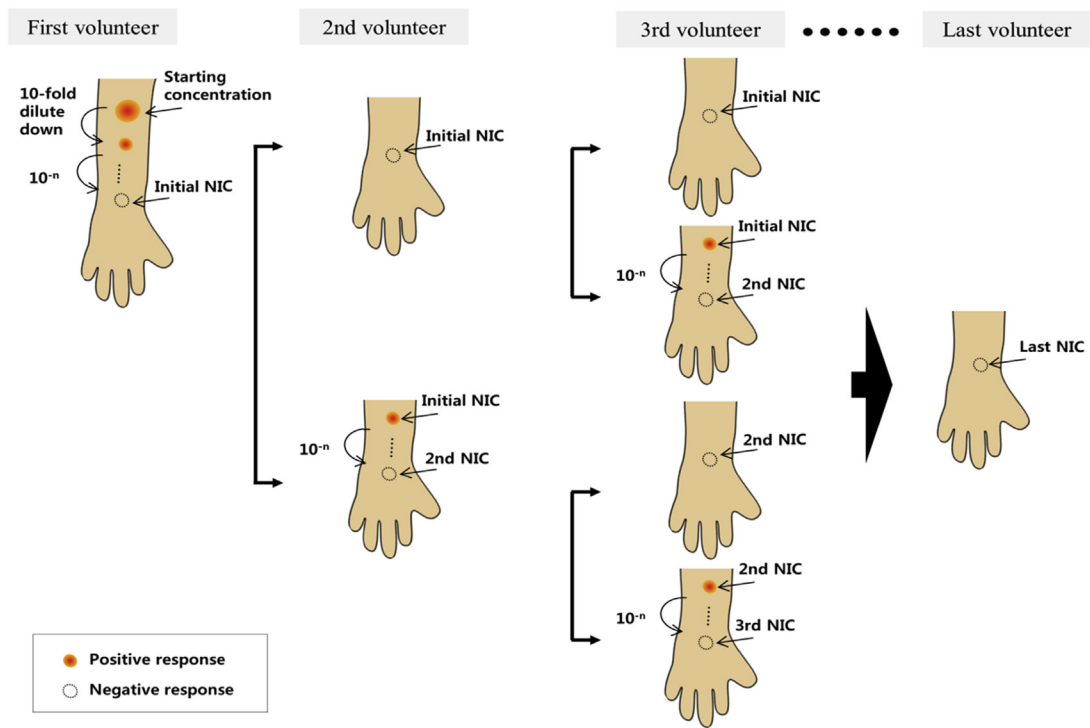


FIGURE E1. Determining NICs for 17 commonly used antibiotics.

TABLE E1. Summary of previous reports on the NIC of various antibiotics

Authors	Year	No. of control	Tested drugs (suggested NIC)
Barbaud et al ^{E1}	2001	20	Penicillin G (5106 U/mL), amoxicillin/clavulanic acid (250 mg/mL), cloxacillin (200 mg/mL), cefotaxime (250 mg/mL), cefotiam (100 mg/mL), ciprofloxacin (0.2 mg/mL), ofloxacin (5 mg/mL), erythromycin (5 mg/mL), cotrimoxazole (400 mg/mL), spiramycin (3750 U/mL), doxycycline (20 mg/mL)
Empedrad et al ^{E2}	2003	25-30	Cefotaxime (10 mg/mL), cefuroxime (10 mg/mL), cefazolin (33 mg/mL), ceftazidime (10 mg/mL), ceftriaxone (10 mg/mL), tobramycin (4 mg/mL), ticarcillin (20 mg/mL), clindamycin (15 mg/mL), gentamicin (4 mg/mL), cotrimoxazole (0.8 mg/mL), levofloxacin (0.025 mg/mL), erythromycin (0.05 mg/mL), azithromycin (0.01 mg/mL), nafcillin (0.025 mg/mL), vancomycin (0.005 mg/mL)
Testi et al ^{E3}	2010	5-215	Penicillin G (10,000 IU/mL), amoxicillin/clavulanic acid (20 mg/mL), aztreonam (2 mg/mL), cefuroxime (20 mg/mL), ceftriaxone (20 mg/mL), cefotaxime (20 mg/mL), ceftazidime (20 mg/mL), cefazolin (20 mg/mL), cefepime (2 mg/mL)

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