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The Global Implications of the Gentamicin Histamine Contamination: Sorting Fact from Fiction

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On 6 October 2017, the Therapeutics Goods Administration (TGA), in conjunction with Pfizer Australia, released a statement to recall 10 batches of Gentamicin Infection BP (80 mg) in 2-ml Steriluer ampoules due to the finding that these batches may have contained higher than expected amounts of histamine, a residual from the manufacturing process (1). Other countries, including the United Kingdom and Canada, also put out similar regulator warnings (2, 3). Considering that gentamicin hypersensitivity is rarely reported (4, 5), we reviewed gentamicin-associated adverse drug reactions (ADRs) during the period 2016 to 2017 in Australia and present a case of confirmed immediate (IgE-mediated) gentamicin hypersensitivity.

TGA records were searched for the term "gentamicin" for the period 2016 to 2017. A total of 41 reports were identified; 17 were consistent with an immediate hypersensitivity due to either IgE-mediated allergy or higher than expected amounts of histamine, defined as the presence of rash, urticaria, swelling, angioedema, hypotension, or

TABLE 1 Demographics and clinical characteristics of patients with a gentamicin ADR reported to the TGA (2016 to 2017) with an IgE-mediated allergy phenotype[a]

Clinical characteristic (n = 17)	No. (%) of patients[b]
Male patients	9 (53)
Median age, yr (IQR)	51 (38–66)
Another antibiotic implicated in causality[c]	8 (47)
Beta-lactam antibiotic implicated[d]	7 (42)
Other[e]	2 (12)
No. of patients with gentamicin ADR after first dose[f]	16 (94)
Median gentamicin dose (mg) pre-adverse event (IQR)	300 (240–400)
i.v. gentamicin administration	16 (100)
ADR onset within $5t_{1/2}$ of gentamicin dose	15 (94)
Anaphylaxis	6 (35)
Rash NOS/urticaria	13 (76)
Angioedema	9 (56)
Respiratory involvement	5 (29)
Adrenaline administered (i.m., i.v., or inhaled)	5 (29)
Intensive care admission	3 (19)
Mortality (inpatient)	0 (0)

[a]NOS, not otherwise specified; i.m., intramuscular; i.v., intravenous; ADR, adverse drug reaction; IQR, interquartile range; $5t_{1/2}$, five half-lives.
[b]Except as noted otherwise in column 1.
[c]Patients where another antibiotic was administered in the peri-ADR period in addition to gentamicin.
[d]Amoxicillin or ampicillin (n = 4), flucloxacillin (n = 3).
[e]Vancomycin (n = 1), clindamycin (n = 1).
[f]One patient reported a reaction following the third dose.

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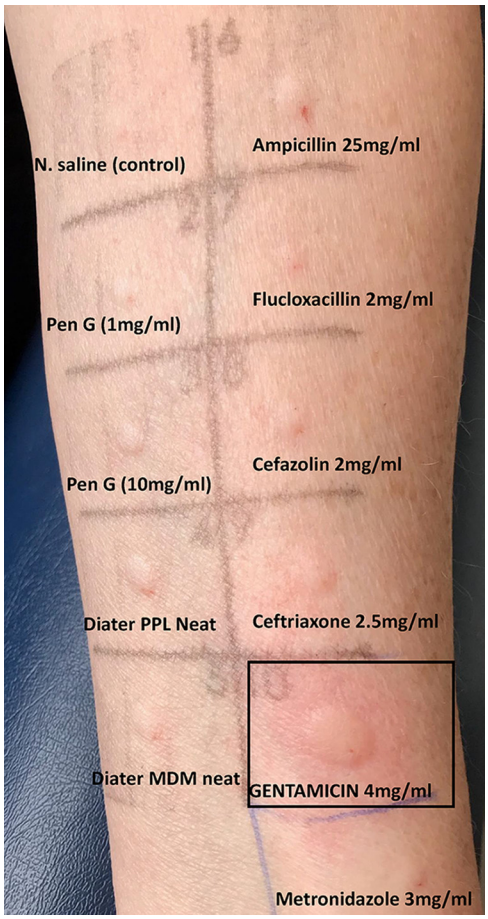

FIG 1 Positive skin test in response to gentamicin (4 mg/ml) in a patient with a history of presumed gentamicin anaphylaxis (4-mm increase in wheal and 28-mm flare). PPL, benzylpenicil-loyl-poyl-L-lysine; MDM, minor determinant mixture; Pen G; benzylpenicillin.

anaphylaxis. Gentamicin was the single implicated drug in 9 cases (53%) compared to only 2 reports for the period from 2014 to 2015. The most commonly implicated alternative drug was a beta-lactam antibiotic (7 cases; 42%) (Table 1). The clinical characteristics of TGA-reported cases are presented in Table 1. Within this cohort was a middle-aged female who developed anaphylaxis at Austin Health (Victoria, Australia) in late 2017 following empirical treatment for diverticulitis with intravenous ampicillin (2 g) and oral metronidazole (400 mg) and, 1 h later, intravenous gentamicin (320 mg). Within 2 h of gentamicin administration, she was noted to be tachycardic with a prominent truncal erythematous rash, angioedema, and hoarse voice, symptoms that responded to intramuscular adrenaline (0.3 mg), nebulized adrenaline, intravenous hydrocortisone (250 mg), and intravenous promethazine (25 mg). She had no history of drug allergy. Her single tryptase level determination, performed 2 h after anaphylaxis onset, was 9.7 μg/liter (0.0 to 11.4). The case was referred to the hospital's multidisciplinary ADR Committee and subsequently to the TGA.

She proceeded to skin prick (SPT) and intradermal (IDT) testing 3 months after anaphylaxis, utilizing a published beta-lactam skin testing protocol (6). In addition, SPT and IDT in response to gentamicin (4 mg/ml, nonrecalled batch) and metronidazole (3 mg/ml) were performed utilizing available nonirritating concentrations (7). The only positive result was noted in response to gentamicin (IDT) (Fig. 1). She subsequently tolerated phenoxymethylpenicillin (250 mg) and amoxicillin (250 mg).

We noted a higher-than-predicted number of gentamicin ADRs with an immediate hypersensitivity phenotype for the period from 2016 to 2017 that is potentially attrib-

utable to higher-than-expected amounts of histamine. This may be a phenomenon unknown to many physicians and pharmacists from countries with affected gentamicin batches. Although gentamicin was the primarily implicated drug in the majority of the identified cases reported to TGA, other drugs administered concurrently cannot be excluded from causality. The confirmed case of immune-mediated gentamicin anaphylaxis, however, emphasizes the critical importance of evaluating these patients for true IgE-mediated allergy. While increased histamine batch contamination cannot be excluded, the strongly positive intradermal test and clinical anaphylaxis features ensure future drug avoidance for the described patient, showing that clinicians should be vigilant when treating patients reporting histories of gentamicin immediate hypersensitivity rather than simply attributing this to higher-than-expected amounts of histamine in the product.

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REFERENCES

1. Therapeutics Goods Administration. 2017. Recall: potential for allergic reactions due to higher than expected amounts of histamine. Therapeutics Goods Administration, Symonston, Australia. https://www.tga.gov.au/alert/gentamicin-injection-bp-80-mg-2-ml-steriluer.
2. Health Canada. 2018. Gentamicin Injection USP (10 mg/ml and 40 mg/ml): potential for adverse reactions with 12 lots contaminated with histamine. Health Canada, Ottawa, Ontario, Canada. http://healthycanadians.gc.ca/recall-alert-rappel-avis/hc-sc/2017/63768a-eng.php.
3. Medicines and Health Care Regulatory Agency. 2017. Gentamicin: potential for histamine-related adverse drug reactions with some batches. Medicines and Health Care Regulatory Agency, London, United Kingdom. https://www.gov.uk/drug-safety-update/gentamicin-potential-for-histamine-related-adverse-drug-reactions-with-some-batches.
4. Hall FJ. 1977. Anaphylaxis after gentamycin. Lancet 2:455.
5. Schulze S, Wollina U. 2003. Gentamicin-induced anaphylaxis. Allergy 58:88–89. https://doi.org/10.1034/j.1398-9995.2003.23710_5.x.
6. Trubiano JA, Thursky KA, Stewardson AJ, Urbancic K, Worth LJ, Jackson C, Stevenson W, Sutherland M, Slavin MA, Grayson ML, Phillips EJ. 2017. Impact of an integrated antibiotic allergy testing program on antimicrobial stewardship: a multicenter evaluation. Clin Infect Dis 65:166–174. https://doi.org/10.1093/cid/cix244.
7. Empedrad R, Darter AL, Earl HS, Gruchalla RS. 2003. Nonirritating intradermal skin test concentrations for commonly prescribed antibiotics. J Allergy Clin Immunol 112:629–630. https://doi.org/10.1016/S0091-6749(03)01783-4.