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The use of topical antibiotics based on National Database of Health Insurance Claims and Specific Health Checkups of Japan (NDB) Open Data in 2017

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Abstract

The national action plan on antimicrobial resistance (AMR) in Japan emphasizes the importance of understanding antimicrobial use (AMU). Some studies have been conducted on oral and parenteral AMU in Japan. However, there are few studies on the use of topical antimicrobials, such as in dermatology and ophthalmology. Therefore, the purpose of this study was to investigate topical AMU in Japan. Data on AMU in dermatology and ophthalmology were obtained from the 2017 National Database of Health Insurance Claims and Specific Health Checkups of Japan Open Data. The number of dermatological products used was 58,396,530 in 2017. The proportion of betamethasone/gentamicin was 50.5% and that of gentamicin 16.7%, whereas that of the ingredient quantity in gentamicin was 7.8%. It was suggested that topical AMU should be evaluated by the number of products. The number of ophthalmological products used was 24,655,653 in 2017, and the proportion of quinolones was 95.9%. The high prescription rate of quinolones may cause an increase in quinolone resistance in the ophthalmologic field. Topical AMU, which is a potential “blind spot” in the measures against AMR, needs to be continuously monitored, together with systemic AMU.

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Introduction

Antimicrobial resistance (AMR) is an increasingly serious global challenge and is one of the greatest potential threats to human health (1). In 2014, 114 of 194 World Health Organization (WHO) member states reported the detection of at least one drug-resistant bacterium. Alarming, 89 WHO member states reported the detection of more than five types of drug-resistant bacteria (2). Consequently, the World Health Assembly endorsed the Global Action Plan on Antimicrobial Resistance in 2015. Japan developed a national action plan for AMR, presenting priorities for implementation to promote AMR measures in 2016. Because antibiotic use is associated with drug-resistant bacteria, the monitoring of antimicrobial use (AMU) has been strengthened since then (3). There have been some studies on oral and parenteral AMU in Japan (1,4).

However, there are few studies on topical AMU worldwide, including Japan. Two clinical departments frequently prescribe topical antimicrobials, that is, eye drops in ophthalmology and ointments in dermatology. Although ophthalmological antibiotics have not been proven useful for perioperative prophylaxis (5), they are often used in clinics. Furthermore, an increase in drug-resistant bacteria has been reported in dermatology (6). In the United States, methicillin-resistant *Staphylococcus aureus* (MRSA) isolated from outpatients in dermatology had not been reported before 1987 (5). However, MRSA has recently accounted for more than 50% of community-associated *Staphylococcus aureus* infections in dermatology (5). Thus, the evaluation of topical AMU in ophthalmology and dermatology is of paramount importance.

AMU is often studied using the insurance claims database and sales data (7,8). The National Database of Health Insurance Claims and Specific Health Checkups of Japan (NDB) is an insurance claim database that contains most of the available data in the national healthcare insurance system. However, direct access to data is limited to researchers who can provide a highly secure environment (9). Recently, the Ministry of Health, Labour and

Welfare published NDB Open Data, which is based on Japanese healthcare system statistics and its health condition (9). NDB Open Data is suitable for an easy and comprehensive understanding of medical care in Japan, and some studies have revealed trends in drug use or the number of surgeries in Japan based on NDB Open Data (10,11).

Therefore, the purpose of this study was to investigate trends in the usage of topical antibiotics in Japan based on NDB Open Data.

Materials and Methods

Data collection

Topical antibiotic data were obtained from NDB Open Data (12). The surveillance period was 2017. NDB Open Data provides the top 100 prescriptions in each efficacy category, and the 101st and lower drugs have been excluded. Additionally, the number of products of 1,000 or fewer is truncated.

Topical antibiotics used in dermatology and ophthalmology were examined in this study. Regarding ophthalmology, eye drops were investigated, and eye ointments and nasal drops were excluded. Eye drops were classified according to pharmacological class. Table 1 shows the anatomical therapeutic chemical (ATC) codes of the topical antibiotics used in this study. Systemically administered antibiotics (J01X) may be classified into other groups if their target is exclusively local (13). Therefore, sulfadiazine, polymyxin B, tosufloxacin, cefmenoxime, and dibekacin, defined as J01X for systemic use, were assigned to the original codes D06BA, D06AX, S01AE, S01AA, and S01AA, respectively.

Evaluation of topical AMU

NDB Open Data are aggregated by product name without information regarding the ingredients. Ingredient information was combined with the data using the topical agent

master published by the Ministry of Health, Labour and Welfare, Japan (14). NDB Open Data provides the total drug quantity prescribed using the unit defined in the National Health Insurance (NHI) drug price standard listing (9). Topical antibiotics are often prescribed using the product unit. Thus, topical antibiotic use was evaluated based on “the number of products” in this study. Information regarding the product unit was combined into data using the Pharmaceutical HOT Code Master provided by the Medical Information System Development Center (15). If multiple product units were present, the minimum product unit was given. The number of products was calculated by dividing the total drug quantity provided by NDB Open Data by the product unit.

The following equation was used:

The number of products (n)

= total drug quantity (g, mL, sheet, or unit) / minimum product unit (g, mL, sheet, or unit)

AMU was stratified by age group to assess differences in use by age. The number of products was divided by the population of each age group and corrected to per 1,000 people. Population data were obtained from the Statistics Bureau of Japan (16).

Amounts of ingredients in dermatological antibiotics were also provided. The combination drugs were calculated for each ingredient. Polymyxin B and bacitracin were excluded because they could not be indicated in grams. Amounts of ingredients were calculated by multiplying the total drug quantity by the concentration.

The following equation was used:

The amount of ingredient (ton)

= (total drug quantity [g, mL, or sheet]) (concentration [g/g, mL, or sheet]) / 1,000,000

The number of ophthalmic surgeries

To examine the relationship between the number of ophthalmologic surgeries and antibiotic use in ophthalmology, ophthalmic surgery data were obtained from NDB Open Data in 2017 (12). The total number of ophthalmic surgeries was the sum of each surgery type in the field of ophthalmology. Lens surgeries were classified into six types of lens reconstruction, namely, “lens reconstruction for intraocular lens insertion,” “lens reconstruction without intraocular lens insertion,” “lens reconstruction with the insertion of a sutured lens,” “lens reconstruction through a planned posterior capsulotomy,” “lens reconstruction with lens sac expansion ring and sutures,” and “lens reconstruction without lens sac expansion ring and sutures.” Vitreous surgeries were classified into seven types of vitreous surgery, including “vitreous injection/suction,” “vitreous resection,” “vitrectomy including retinal adherent tissue (intraocular endoscopy),” “vitreous replacement,” “vitreous stalk microscopic dissection,” “microscopic dissection of the vitreous stalk including retinal adherent tissue,” and “proliferative vitreoretinopathy surgery.” Overall ophthalmic surgeries and lens/vitreous surgeries were analyzed separately because antibiotic prophylaxis has been recommended for lens/vitreous surgeries (17).

Ethical consideration

NDB Open Data is anonymized open data and does not include individual patient information. Thus, ethical review and informed consent do not require.

Results

Topical AMU in 2017

The investigated antibiotics in dermatology, which were assigned ATC codes D06AX, D06BXX, D07C, and D10AX, included 17 components of 49 items. Fig. 1 shows topical

AMU. The number of dermatological products used was 58,396,530 (Fig. 1a). The proportion of betamethasone/gentamicin was 50.5% and that of gentamicin 16.7%. The proportions of nadifloxacin and clindamycin were 9.4% and 6.8%, respectively. However, the ingredient quantity in dermatological antibiotics was 3.5 ton, and the proportion of gentamicin was 7.8% (Fig. 1b). The ingredient quantities of nadifloxacin and clindamycin were 18.1% and 12.5%, respectively.

The investigated antibiotics in ophthalmology, which were classified as ATC code S01A anti-infectives, included eight components of 31 items. Levofloxacin accounted for 18 of 31 items. Fig. 1c shows the number of antibiotic products in ophthalmology. The number of antibiotic products in ophthalmology was 24,655,653. The proportion of quinolones (levofloxacin, gatifloxacin, moxifloxacin, ofloxacin, and tosufloxacin) was 95.9%, followed by that of third-generation cephalosporins (cefmenoxime; 4.0%). The total aminoglycoside proportion (dibekacin and tobramycin) was less than 0.1%.

Topical AMU stratified by age group

Fig. 2 presents the number of antibiotic products in dermatology stratified by age group. Antibiotic use in dermatology increased significantly from 70 years of age and older. Betamethasone/gentamicin was predominantly used in all age groups, except for the 15–19-year age group. The percentage of clindamycin use was high in the 10–30-year age range, ranging from 10.6% to 30.6%, and low in other age groups, that is, less than 7.9%. The percentage of fusidic acid use was high in the 0–9-year age group.

Fig. 3 shows topical AMU in ophthalmology and the number of ophthalmic surgeries stratified by age group in 2017. Antibiotic use in ophthalmology was higher among those aged 0–9 years and increased significantly from 60 years of age and older. Aminoglycosides (dibekacin and tobramycin) have been used in infants and the elderly and have rarely been

used in other generations. The overall number of ophthalmic surgeries was 2,934,702, and that of lens surgeries and vitreous surgeries was 1,179,822 in 2017. Although AMU increased with age after 60 years of age, the number of surgeries peaked in the 75–79-year age group and decreased thereafter.

Discussion

Drug-resistant bacteria are a global problem (1). There have been some studies on oral and parenteral AMU (1,4). Topical AMU may also be involved in the emergence of drug-resistant bacteria. However, trends in topical AMU have not been clarified. This is the first study to investigate topical AMU based on NDB Open Data.

The number of antibiotic products used in dermatology was 58,396,530 in 2017. The proportion of ingredients in gentamicin was 7.8%, despite the proportion of the number of products in betamethasone/gentamicin and gentamicin being 50.5% and 16.7%, respectively. This is because all gentamicin products contain only 0.1% gentamicin. Although the AMU of oral and parenteral antibiotics have been evaluated by the amount of ingredient (1, 8), it was suggested that topical AMU should be evaluated by the number of products.

According to a report on dermatological disorders in Japan, eczema was the most common (approximately 40%) (18). Topical products containing gentamicin may be used for secondary infections, such as eczema, in addition to infections. However, the data source we used did not allow us to clarify the purpose of use. Even so, the use of gentamicin products should be closely monitored in terms of their purpose of use to prevent the inappropriate use of these products.

The percentage of clindamycin use was high in the 10–30-year age group. Clindamycin has been indicated for acne vulgaris and has also been recommended in guidelines (19). The prevalence of acne is reportedly higher in the 10–30-year age group than in other age groups (18). Therefore, it is likely that clindamycin is more commonly used in this age group. In recent

years, the antimicrobial resistance of acne bacteria has also been a problem (20), and clindamycin use may need to be closely monitored.

The percentage of fusidic acid use was high in the 0–9-year age group. Fusidic acid is often used for infectious impetigo, which commonly affects children (21,22). *Staphylococcus aureus* (*S. aureus*) is the most common causative bacterium of infectious impetigo. According to Japanese guidelines, because more than half of *S. aureus* strains are resistant to gentamicin, the use of nadifloxacin or fusidic acid has been recommended (21). However, the increased use of fusidic acid and corresponding increase in *S. aureus* resistance to fusidic acid have been reported (23,24). It should be noted that topical antibiotic use is also involved in drug-resistant bacteria.

In this study, we also examined AMU in ophthalmology as well as dermatology. Quinolones accounted for 95.9% of the antibiotics used in ophthalmology. Guidelines recommend quinolones as the first-line treatment for most ocular infections, such as hordeolum, blepharitis, lacrimal pouchitis, conjunctivitis, and keratitis (21). This is presumably the main reason for the high prescription rate of quinolones.

Conjunctivitis reportedly accounts for nearly 80% of all ocular infections (25). Because conjunctivitis is common in infants, school children and the elderly (26), AMU in ophthalmology has been considered to be higher among patients aged 0–9 years and those aged 60 years and older. In addition, antibiotic eye drops are used to prevent gonococcal ophthalmitis in newborns. This was considered one of the reasons for the high AMU in the 0–4-year age group. The combination of erythromycin and colistin has previously been used for prophylaxis of gonococcal ophthalmitis in newborns (27). However, because the combination drug of erythromycin and colistin was discontinued in 2016, it was estimated that quinolones were used as alternative drugs.

Between the ages of 15 and 79 years, AMU in ophthalmology increased with an increase in

the number of ophthalmic surgeries. These results suggest that eye drops are often used to prevent perioperative infection. Although preoperative antibiotic use has been recommended before lens reconstruction and vitreous surgeries in Japanese guidelines (17), there has been no consensus regarding the postoperative period. Since resistant bacteria were also observed after short-term use during the perioperative period in a previous study (28), it is necessary to establish an appropriate method of antibiotic use during the perioperative period in ophthalmology.

Although the number of surgeries peaked in the 75–79-year age group and decreased thereafter, AMU increased. In patients aged 80 years and older, antibiotic eye drops could potentially be used for purposes other than perioperative infection prevention. Based on the epidemiology of conjunctivitis (25,26), the use of antibiotics for conjunctivitis in the elderly may become an issue. *Corynebacterium macginleyi* (*C. macginleyi*) is one of the causative bacteria of conjunctivitis. In recent years, the resistance rate of *C. macginleyi* to quinolones has been reported to be higher in Japan than in other countries (29,30). This may be due to the fact that quinolone eye drops are widely used in Japan. *C. macginleyi* with conjunctivitis has been reported to be sensitive to cepheems and aminoglycosides (31). It may be necessary to consider the use of cepheems or aminoglycosides after confirming susceptibility.

This study has certain limitations due to the characteristics of NDB Open Data. First, the number of products of 1,000 or less is truncated, resulting in differences between the overall results and those stratified by age group. Second, the number of products and information regarding individual patients, such as disease diagnosis and the results of bacterial cultures, were not available. Furthermore, topical antibiotics were uncertain actual used or not. Nevertheless, NDB Open Data is free and open to the public and has been used in many other studies (9–11). NDB Open Data has been useful for understanding topical antibiotic use in Japan. This study revealed topical antibiotic use in Japan, which tends to be a “blind spot” in measures

against antimicrobial resistance. In the future, it may be necessary to conduct continuous and detailed investigations on topical antibiotic use based on other databases, such as insurance claim data. Furthermore, the association between topical antibiotic use and resistant bacteria also needs to be investigated.

This study is the first to elucidate the trends in topical antibiotic use in Japan. Large doses of gentamicin were prescribed at low concentration in dermatology. In addition, quinolones had a high prescription rate in ophthalmology. Our findings suggest the importance of continuously evaluating the use of topical antibiotics in Japan.

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Conflict of Interest

Yuichi Muraki received an honorarium from Pfizer Japan, Inc., for lecturing. The other authors declare no conflicts of interest.

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Figure Legends

Figure 1. Topical AMU in 2017 based on NDB Open Data

- a. The number of antibiotic products used in dermatology
- b. The amount of antibiotic ingredients used in dermatology
- c. The number of antibiotic products used in ophthalmology

AMU; antimicrobial use

NDB; the National Database of Health Insurance Claims and Specific Health Checkups of Japan

Figure 2. Topical AMU in dermatology stratified by age class in 2017

AMU; antimicrobial use

Figure 3. Topical AMU in ophthalmology and the number of ophthalmic surgeries stratified by age class in 2017

*The number of ophthalmic surgeries for 90–94-year olds includes values for 95 years and older.

AMU; antimicrobial use

Table 1. ATC topical-antibiotic codes

Dermatology		Ophthalmology	
Ingredients	ATC group (4th level)	Ingredients	ATC group (4th level)
Betamethasone / Gentamicin	D07CC	Levofloxacin	S01AE
Gentamicin	D06AX	Gatifloxacin	S01AE
Nadifloxacin	D10AF	Moxifloxacin	S01AE
Clindamycin	D10AF	Ofloxacin	S01AE
Neomycin	D06AX	Tosufloxacin	S01AE
Neomycin / Bacitracin	D06AX / D06AX	Cefmenoxime	S01AA
Fusidic acid	D06AX	Dibekacin	S01AA
Silver sulfadiazine	D06BA	Tobramycin	S01AA
Sulfadiazine	D06BA		
Ozenoxacin	D06AX		
Tetracycline	D06AA		
Neomycin / Chloramphenicol	D06AX / D06AX		
Neomycin / Trypsin	D06AX / D03BA		
Neomycin / Hydrocortisone	D07CA		
Oxytetracycline / Polymyxin B	D06AA / D06AX		
Polymyxin B	D06AX		
Chloramphenicol	D06AX		

ATC; The Anatomical Therapeutic Chemical classification system

Figure 1. Topical AMU in 2017 based on NDB Open Data

AMU; antimicrobial use

NDB; the National Database of Health Insurance Claims and Specific Health Checkups of Japan

Figure 2. Topical AMU in dermatology stratified by age class in 2017

AMU; antimicrobial use

Figure 3. Topical AMU in ophthalmology and the number of ophthalmic surgeries stratified by age class in 2017

* The number of ophthalmic surgeries for 90-94-year olds includes values for 95 years and older.

AMU; antimicrobial use