Comparative study of tosufloxacin tosilate fine granules 15% for pediatrics: MEIJI® versus Ozex®

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In this study, we compared the efficacy, adverse event incidences, and medication compliance of MEIJI® (T group) with those of Ozex® (O group) tosufloxacin tosilate fine granules. Tosufloxacin tosilate fine granule was effective in all but one case (32/33) while the time to defervescence was within 2 days of drug administration in both groups (T and O groups, 1.31 and 1.92 days, respectively). The time to cough improvement was within 3 days of drug administration in both groups (T and O groups, 2.27 and 2.64 days, respectively). Adverse events were observed in 7.3% and 14.1% of the T and O groups (6/82 and 10/71), respectively. The medication compliance was good in both groups and, overall, the mean rate of administration of the T and O groups was 93.8% and 97.0%, respectively. The rate of complete administration was 87.8% (72/82) and 91.5% (65/71) in the T and O groups, respectively. No significant changes were observed between the two groups in efficacy, adverse event incidences, and medication compliance. Therefore, tosufloxacin tosilate fine granule 15% for pediatrics (MEIJI®) may be equivalent to tosufloxacin tosilate hydrate 15% for pediatrics (Ozex®) in efficacy, adverse event incidences, and medication compliance.

Introduction

Tosufloxacin tosilate fine granule 15% for pediatrics (MEIJI®) is a generic formulation of the drug Ozex® (tosufloxacin tosilate hydrate 15% for pediatrics), which was released on June 19, 2015, in Japan. Generic drugs are thought to have the same effectiveness and incidences of adverse events. However, factors affecting patient drug compliance (the taste and frequency of medicine administration) may differ between the original brand and generic drugs, particularly for children and, therefore, their effectiveness and adverse event incidences may also differ. Tosufloxacin tosilate is the only new quinolone that can be used for treating pediatric pneumonia and otitis media and is usually used against other antibiotic-resistant pathogens. It also is thought to

decrease hospitalization due to pneumonia in children[1]. Therefore patient compliance to drugs is thought to be extremely important to avoid increasing the incidence of antibiotic-resistant bacteria.

The effectiveness and incidence of adverse events of Ozex® have been reported previously[2, 3], but not that of MEIJI®. In addition, only one study comparing the effectiveness of MEIJI® with that of Ozex® *in vitro* and *in vivo* (mice pneumonia model) has been reported[4]. Therefore, the purpose of this study was to investigate the effectiveness and incidences of adverse events of MEIJI® and subsequently compare it with those of Ozex® in a population of Japanese children.

Patients and Methods

This study was conducted according to the Helsinki Declaration and performed after the written informed consent of patients, their parents, or both was obtained. The study design was approved by the appropriate ethics review board of our clinic (the approval code: AC1501).

Eligibility Criteria

The eligibility criteria were as follows:

1) Age: 1–14 years
2) Clinically diagnosed with bacterial pneumonia, otitis media, or both.
3) Induction of tosufloxacin tosilate therapy was considered appropriate.
   a) Previous antibiotic therapies were not effective, and atypical pneumonia could not be denied.
   b) First-line drugs (e.g., macrolides) could not be used because of the existence of drug allergies, severe adverse events, or administration difficulties.
   c) The family members of the patients exhibited a similar clinical course as that described in a).

Exclusion Criteria

1) A history of allergy to tosufloxacin tosilate.
2) Use of other generic tosufloxacin tosilate fine granule drug formulations (e.g., Takada and Sawai).

Epilepsy and arthralgia were not excluded with the condition that the merit of medication use outweighed the demerits of use and informed consent was acquired from the patients, their parents, or both.

Bacterial pneumonia

Bacterial pneumonia was defined as follows:

1) Typical clinical symptoms such as fever, cough, and sputum.
2) Infiltrates observed in chest X-rays.
   Fulfillment of both 1) and 2) above or:
3) Patients who exhibited a similar clinical course to that of a family member already diagnosed with pneumonia.
4) Cases of viral infection with a suspicion of mixed bacterial infection as evidenced by signs such as prolonged clinical course, productive cough, dense infiltrates (i.e., “consolidation”) visible on diagnostic imaging scans such as chest X-rays.

However, since viral pneumonia may be included using these criteria, the evaluation of efficacy was done for only pathogen-identified cases.

Otitis media

Otitis media was defined as follows:

1) Typical clinical symptoms such as ear pain, fever, and discolored nasal discharge.
2) Confirmation of eardrum infection using an otoscope.
   Fulfillment of both 1) and 2).

Detection of pathogens

1) Culture of respiratory secretions including sputum as well as ear and nasal cavity secretions.
2) *Mycoplasma pneumoniae*:
   Positive reactions using antigen detection kits (Ribotest, Asahi Kasei Pharma Co.).
   Single serum antibody (particle agglutination method): × >320[5)]
3) *Streptococcus pneumoniae*:
   Positive culture with respiratory secretion.
   Positive reaction using urine antigen detection kit (BinaxNOW *Streptococcus pneumoniae* test, Alere Medical Co., Ltd.)
4) *Bordetella pertussis* (Pertussis, diagnosed later):
   Single serum antibody (PT-IgG): >100 EU/mL[6)].

Other viral antigen detection kits also were used (respiratory syncytial virus [RSV], human metapneumovirus, influenza virus, and adenovirus).

Efficacy

The efficacy was evaluated according to the criteria of the Japanese Society of Chemotherapy[7)]. However, fever and cough were evaluated separately.

Namely, fever: the effectiveness was defined as the occurrence of defervescence within 3 days from starting tosufloxacin tosilate fine granule treatment.

Cough: the effectiveness was defined as cough improvement occurring within 7 days from

starting tosufloxacin tosilate fine granule treatment because cough improvement is usually delayed.

“Overall effectiveness” was defined as positive confirmations using either clinical symptoms (fever, cough, wheezing, and dyspnea) or clinical examination (X-rays and otoscope). The performance of an X-ray re-examination when either infiltrates or consolidation regressed was defined as an effective response. As mentioned above, the efficacy was evaluated only in pathogen-identified cases.

Adverse events

The adverse events were also evaluated according to the criteria of the Japanese Society of Chemotherapy[7], which were classified into the following five groups:

- No medication/complete: No treatments for adverse events was needed, and medication could be administered completely.
- Medication <4 days/complete: Treatment of adverse events was needed within 3 days, but medication could be administered completely.
- Medication ≥4 days/complete: Treatment for an adverse event was needed over 3 days, but medication could be administered completely.
- Drug discontinuation/no medication: Tosufloxacin tosilate fine granule had to be discontinued because of incidences of adverse events, but no treatments were needed.
- Drug discontinuation/medication needed: Tosufloxacin tosilate fine granule had to be discontinued because of incidences of adverse events and medication was needed.

Medication compliance

Patient medication compliance was evaluated according to the criteria of the Japanese Society of Chemotherapy[7], based on the following four classification groups:

- Complete (100%): This group consisted of patients who could take the complete tosufloxacin tosilate fine granule regimen.
- Almost 100% complete: This group included patients who were sometimes unwilling to take the tosufloxacin tosilate fine granule but could take it almost completely for the most part.
- Impossible to administer: The group included patients who could not take the tosufloxacin tosilate fine granules.
- Discontinuation due to ineffectiveness or adverse events: This group included cases of patients who had to stop tosufloxacin tosilate fine granule because of its ineffectiveness or incidences of adverse events.

The projected number of cases was at least 100 for each group, and the allocation was equivalently performed but was based on the willingness of patients, their parents, or both.

The effectiveness and adverse event evaluations were determined during the patients' revisit or using the questionnaire or telephone interview. The cases that used generic drugs of other pharmaceutical companies were also excluded by similar way.

Statistical analysis

The student *t*-test and chi-square (χ^2) test were used to compared the groups treated with MEIJI® and Ozex® (tosufloxacin tosilate hydrate 15% for pediatrics). When confounding factors were observed, the logistic regression analysis was included and a two-sided $P < 0.05$ was considered significant.

Statistical analysis was performed using the JMP® 13 (Statistical Analysis Software, SAS Institute Inc., Cary, NC, USA).

Results

Patient characteristics

From June 2015 to September 2016, 206 patients were enrolled (male : female patients, 105 : 101). However, since some cases had bronchial asthma and complicated bronchial asthma attacks or were in a condition of asthmatic bronchitis at their presentation, steroid use was necessary. Steroid therapy affects fever and cough and, therefore, we excluded cases that used steroid therapy. Finally, 153 patients were treated with MEIJI® and Ozex® (T and O groups, 82 and 71 cases, respectively) and their characteristics are listed in Table 1. Among the clinical factors, age

Table 1. Patient characteristics

	Tosufloxacin tosilate, Meiji ® (n = 82)	Ozex® (n = 71)	*P*-value
Age	4.6 (± 0.36)	6.2 (± 0.39)	0.0017*
Sex	M:F = 41:41	M:F = 34:37	0.8715
Body weight at birth (g)	3024.5 (± 51.1)	3047.2 (± 55.3)	0.3811
Diagnosis: Pneumonia	92.7% (76/82)	85.9% (61/71)	0.1946
Otitis media	2.4% (2/82)	5.6% (4/71)	0.4168
Both	4.9% (4/82)	7.0% (5/71)	0.7339
Underlying diseases	7.3% (6/82)	9.9% (7/71)	0.7725
Pretreatment (antibiotics)	53.7% (44/82)	62.0% (44/71)	0.3282
Vital signs: B.T. (℃)	37.8 (± 0.11)	37.5 (± 0.12)	0.9534
B.P. (mmHg)	87.0 (± 1.26)/57.7 (± 1.10)	87.0 (± 1.36)/56.6 (± 1.19)	0.4964/0.7374
H.R. (/min)	122.1 (± 2.81)	110.2 (± 3.02)	0.9978
SpO_2 (%)	97.7 (± 0.16)	97.6 (± 0.18)	0.5426

Mean (± standard error); body weight at birth (n = 152), B.T. (n = 148), B.P. (n = 146), H.R. (n= 151), SpO_2 (n = 151)

was significantly lower in the T group than it was in the O group (mean 4.6±0.36 and 6.2±0.39 years, respectively, *P*=0.0017). The other clinical factors were equivalent between the two groups. Clinical diagnoses consisted of 137 cases of pneumonia, six cases of otitis media, and nine cases of both pneumonia and otitis media. Underlying diseases were observed in 13 cases, and bronchial asthma was the most commonly seen (69.2% [9/13]). Previous viral infection was observed in three cases (two cases of RSV infections and one case of human metapneumovirus infection). Furthermore, 88 cases were pretreated with antibiotics (macrolides: 60, cephems: 15, penicillins: 10, cephems plus macrolides: three).

Efficacy

The efficacy evaluation is summarized in Table 2. The responsible pathogens were identified in 33 cases. The identified pathogens are as follows; Pneumonia/*Mycoplasma pneumoniae*: 11, *Streptococcus pneumoniae*: 2, *S. pneumoniae* plus *Branhamella catarrhalis*: 2, *Haemophilus influenzae*: 1, *S. pneumoniae*+*H. influenzae*: 1, *S. pneumoniae*+*H. influenzae* (*β*-lactamase-negative ampicillin-resistant, BLNAR): 1, *S. pneumoniae*+*H. influenzae*+*B. catarrhalis*: 1, *Bordetella pertussis*: 1; pneumonia plus otitis media/*S. pneumoniae*: 2, *H. influenzae*: 1, *B. catarrhalis*: 1, methicillin-sensitive *Staphylococcus aureus* (MSSA): 1, *Corynebacterium* sp.: 1, *H. influenzae*+*B. catarrhalis*: 1, *H. influenzae*+*Corynebacterium* sp.: 1; and otitis media/*H. influenzae*: 3, MSSA: 2. Among the pneumonia-inducing pathogens, *M. pneumoniae* was the most frequent (33.3%, 11/33). Infection by macrolide-resistant *M. pneumoniae*, which was defined as being clinically resistant to improvement despite at least 3 days of administration of a macrolide, occurred in 45.5% (5/11, consisting of three and two patients administered clarithromycin and azithromycin hydrate, respectively). The tosufloxacin tosilate fine granule formulation was effective against macrolide-resistant *M. pneumoniae* (in 100%, 5/5). Furthermore, one case of pertussis was identified, which were subsequently diagnosed based on high serum titer (PT-IgG: 160). The tosufloxacin tosilate fine granule formulation was effective in this case with pertussis. Although the number of pathogen-identified cases was low, all cases were effectively treated, except one. The rate of efficacy did not differ significantly between both groups (T and O groups, 94.4% and 100%, respectively). The fever declined rapidly, and the time to defervescence was within 2 days of drug administration in both groups (T and O groups, 1.31 and 1.92 days, respectively). Time to cough improvement was within 3 days of drug administration in both groups (T and O groups, 2.27 and 2.64 days, respectively). Further the only patient considered as “not effectively treated” who was evaluated as a case of *M. pneumoniae* infection, also showed a regression of symptoms following tosufloxacin tosilate treatment (since he needed other therapy for complete resolution, he was evaluated as “not effective”). For otitis media, both drugs were effective in all but one case, which could not be followed-up.

Table 2. Efficacy profiles

	Total	Tosufloxacin tosilate, Meiji® (n = 18)	Ozex® (n = 15)	*P*-value	
				χ^2/t	logistic
Number of patients					
Pneumonia only	20	12	8		
Pneumonia plus otitis media	8	4	4		
Otitis media only	5	2	3		
Efficacy					
Overall		94.4% (17/18)	100% (15/15)	1.0000	0.5370
Pneumonia only[§]		91.7% (11/12)	100% (8/8)	1.0000	0.5863
Pneumonia plus otitis media		100% (4/4)	100% (3/3)[#]	not available	
Otitis media only		100% (2/2)	100% (3/3)	not available	
Clinical symptoms					
Time to defervescence (days)		1.31 (± 0.22)	1.92 (± 0.22)	0.0321*	0.1540
Time to cough improvement (days)		2.27 (± 0.43)	2.64 (± 0.50)	0.2890	0.7771

[§] Including six cases of infection with *Mycoplasma pneumoniae* (macrolide-resistant *M. pneumoniae*; 5/6) previously treated with macrolides (four: clarithromycin, two: azithromycin hydrate)

[#] One case of otitis media was not available (effective for pneumonia in this case)

Adverse events

The adverse event incidences summarized in Table 3 were observed in 7.3% and 14.1% of the T (6/82) and O (10/71) group patients, respectively but overall, no significant differences were observed (corrected *P*=0.2544). Although the number of cases with medication ≥4 days/complete group was significantly higher in the O group than it was in the T group (T and O groups, 0% [0/82] and 4.2% [3/71], respectively, corrected *P*=0.0241), its clinical significance appears to be unclear (because of the small population number). Although adverse events were observed, the rate or number of cases with drug discontinuation was low (T and O groups, 4.9% [4/82] and 2.8% [2/71], respectively). Among the adverse events, gastrointestinal effects were the most common

Table 3. Incidence of adverse events

	Tosufloxacin tosilate, Meiji® (n = 82)	Ozex® (n = 71)	*P*-value χ^2	*P*-value logistic
Overall (percentage)	7.3% (6/82)	14.1% (10/71)	0.1946	0.2544
Completion				
・no medication/complete	2.4% (2/82)	5.6% (4/71)	0.4168	0.2425
・medication < 4 days/complete	0% (0/82)	1.4% (1/71)	0.4641	0.1010
・medication ≥4 days/complete	0% (0/82)	4.2% (3/71)	0.0977	0.0241*
Drug discontinuation				
・drug discontinuation/ no medication	2.4% (2/82)	1.4% (1/71)	1.0000	0.3897
・drug discontinuation/ medication needed	2.4% (2/82)	1.4% (1/71)	1.0000	0.3953
Adverse events				
Completion				
・no medication /complete	1: diarrhea 1: not doing well, lethargy	2: anorexia 1: left parotid gland pain 1: anorexia, headache		
・medication < 4 days/complete	—	1: headache		
・medication ≥ 4 days/complete	—	2: diarrhea 1: abdominal pain, nausea, vomiting, constipation		
Drug discontinuation				
・drug discontinuation/ no medication	1: vomiting 1: anxiety	1: abdominal pain, diarrhea, nausea		
・drug discontinuation/ medication needed	1: abdominal pain, vomiting 1: skin rash	1: diarrhea		

(68.8%, 11/16). All adverse events were reversible and not severe, and no cases were sent to a major hospital.

Medication compliance

The medication compliance was extremely good with both drugs, and no significant changes were observed between the two groups (Table 4). Overall, the mean rates of administration in the T and O groups were 93.8% and 97.0%, respectively. In approximately 90% of cases, the drug regimen administration was complete (T and O groups, 72/82 [87.8%] and 65/71 [91.5%], respectively).

Discussion

This study compared the profiles of MEIJI® and Ozex®. Although the number of evaluated cases was small, the rate of efficacy was approximately 100%. The fever declined within 2 days from drug administration in both groups. Time to cough improvement was within 3 days of drug administration in both groups. This result is comparable to that of previous studies (pneumonia, 100%, otitis media, 97.7%[2], and *M. pneumoniae*, 94.0%[3]). The tosufloxacin tosilate fine granule formulation was effective against macrolide-resistant *M. pneumoniae* (100%, 5/5). Incidentally, one case of pertussis was included and diagnosed later. This patient may have had complicated mixed infections since the X-rays showed dense infiltrates. However, the tosufloxacin tosilate fine granule formulation was also effective in this case of pertussis. Furthermore, 88 cases were pretreated with antibiotics and tosufloxacin tosilate fine granule formulation was also effective for these cases. It was also in agreement with results of previous reports, which showed the effectiveness of tosufloxacin tosilate in antibiotic-resistant infections[3, 8, 9].

The adverse events of both drugs were also comparable, and the overall rate of adverse events was 10.5% (16/153). Although this rate was slightly higher than those of previous reports (2.77%[2] and 3.6%[3]), it was thought to be attributable to the small sample size of this study. Furthermore, no severe adverse events were observed, and the administration of the drug regimen was completed in almost cases (89.5%, 137/153). Almost all adverse events were gastrointestinal (68.8%, 11/16) but drug discontinuation and medication were needed in only three cases (2.0%, 3/153). All cases recovered without sequelae. In addition, the medication compliance of both drugs was good and equivalent. Overall, the percentage of cases that had to discontinue the drug because it was impossible to take, ineffective, or induced adverse events was low (8.5%, 13/153).

Finally, this study has several limitations that are worth mentioning. First, the diagnosis of bacterial pneumonia was uncertain. The diagnosis was based on clinical examinations (clinical symptoms and X-rays), but dense infiltrates could not always be diagnosed as bacterial pneumonia. The rate of pathogen identification was low (21.6%, 33/153). In addition, the pathogens iden-

Table 4.　Medication compliance

	Tosufloxacin tosilate, Meiji ® (n = 82)	Ozex® (n = 71)	*P*-value χ^2	*P*-value logistic
Overall (percentage)	93.8% (± 1.65)	97.0% (± 1.78)	0.1949	0.3671
・100% complete	87.8% (72/82)	91.5% (65/71)	0.5980	0.3383
・Almost 100% complete	1.2% (1/82)	2.8% (2/71)	0.5971	0.0880
・Impossible to take	4.9% (4/82)	0% (0/71)	0.1240	0.0786
・Discontinuation owing to ineffectiveness or adverse events	6.1% (5/82)	5.6% (4/71)	1.0000	0.8774

tified using cultures of respiratory secretion could not be conclusively identified as pathogens (particularly in pneumonia). Second, for the diagnosis of *M. pneumoniae*, the detection of a single serum antibody (particle agglutination method) and rapid antigen test were used. The rapid antigen test showed a sensitivity and specificity of 57.1% and 92.2%, respectively compared to the throat swab culture (package insert first edition, April 2014, Ribotest, Asahi Kasei Pharma Co.) and, therefore, its sensitivity was low. Third, whether administration of the tosufloxacin tosilate fine granule formulation was adequate is questionable under the conditions described above. However, tosufloxacin tosilate fine granules were effective in almost cases in this study; its efficacy was rapid and the clinical course clearly improved in almost cases. Numerous cases in this study used previous antibiotic therapy (57.5%, 88/153), and other cases were considered as moderate grade pneumonia induced by an antibiotic-resistant pathogen (e.g., cases with a similar clinical course to that of a family member already diagnosed with antibiotic-resistant pneumonia) [5]. Finally, the evaluation of efficacy and adverse events was based mainly on the clinical course and few examinations were performed (such as blood sampling). Particularly, multiple blood sampling had not been done in almost case (it is hard to take multiple blood samples from children for medical practitioner). Therefore, there were limitations associated with the evaluation of efficacy and adverse events.

In conclusion, the tosufloxacin tosilate fine granule 15% for pediatrics (MEIJI®) may be equivalent to tosufloxacin tosilate hydrate 15% for pediatrics (Ozex®), in efficacy, adverse events, and medication compliance. Both drugs are extremely effective and safe, particularly for treating bacterial pneumonia and otitis media, as well as other antibiotic-resistant infection. However, their unregulated use should be discouraged to avoid increasing multi-antibiotic-resistant bacterial infections. To the best of our knowledge, this study is the first report showing the efficacy, adverse event incidences, and medication compliance of tosufloxacin tosilate fine granule 15% for pediatrics MEIJI® and the comparison to Ozex®.

Conflict of interest (COI) of the author: No potential COI to disclose.

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