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Pharmacokinetics of Telithromycin Using Bronchoscopic Microsampling after Single and Multiple Oral Doses

Junko Kikuchi, MD; Koichi Yamazaki, MD, PhD; Eiki Kikuchi, MD;
Akitoshi Ishizaka, MD, PhD; Masaharu Nishimura, MD, PhD

From First Department of Medicine, Hokkaido University School of Medicine, Sapporo, Japan (Dr. J. Kikuchi, Dr. Yamazaki, Dr. E. Kikuchi, and Dr. Nishimura); and Department of Medicine, Keio University School of Medicine, Tokyo, Japan (Dr. Ishizaka)

Correspondence and request for reprints should be addressed to:
Koichi Yamazaki, MD, PhD
First Department of Medicine, Hokkaido University School of Medicine,
North 15 West 7 Kitaku, Sapporo 060-8638, Japan
E-mail kyamazak@med.hokudai.ac.jp
Phone +81-11-706-5911
Fax +81-11-706-7899
Abstract

Objectives: Bronchoscopic microsampling (BMS) is a new technique for repeated sampling of bronchial epithelial lining fluid (ELF) to obtain the pharmacokinetic profile of drugs. We analyzed the time versus concentration profiles of telithromycin in bronchial ELF obtained by BMS and compared these finding to those in plasma and alveolar ELF obtained by bronchoalveolar lavage (BAL).

Methods: Bronchial ELF samples were obtained from five healthy subjects using BMS probe at 0, 2, 3, 4, 6, 10 and 24 h after single or multiple oral doses of 600 mg of telithromycin. Alveolar ELF was also obtained by BAL 3 h after single or multiple oral doses of 600 mg of telithromycin.

Results: The areas under the concentration-time curve from 0 to 24 h (AUC0-24) of telithromycin in plasma and bronchial ELF were 2.86 ± 0.60 and 19.5 ± 10.4 mg·h/l after single treatment and 3.60 ± 0.49 and 42.2 ± 22.7 mg·h/l after multiple treatments, respectively. Single and multiple oral doses of telithromycin produced significantly (p<0.05) higher AUC0-24 in bronchial ELF compared to those in plasma. While concentrations in bronchial ELF obtained by BMS were significantly lower than those in alveolar ELF obtained by BAL, they tended to be higher than those in plasma after multiple administration. The telithromycin concentrations obtained by BMS method were very consistent in bronchial ELF at different bronchi at one time point and at the same bronchus at different time points.

Conclusions: Using the BMS technique, we could describe the pharmacokinetics of telithromycin in bronchial ELF. Furthermore, BMS was reasonably validated and reconfirmed to be a feasible and reliable method for measuring antimicrobial concentrations in bronchial ELF.
Key words:
Telithromycin, bronchoscopic microsampling, bronchoscopy, antimicrobial agent, pharmacokinetics, epithelial lining fluid.
Introduction

The efficacy of a drug depends on various factors that include intrinsic potency, protein binding, concentration at the target site (e.g., transport and penetration into bronchial fluid), and pharmacokinetic profile [1]. In bronchial mucosal infections, such as bronchitis and bronchiectasis, pathogens are frequently found within the bronchial lumen. Therefore, the concentration of an effective antibiotic in bronchial epithelial lining fluid (ELF) is an important indicator of clinical success in treating respiratory tract infections [2].

Bronchoscopic microsampling (BMS) is a new technique for repeated sampling of bronchial ELF at either a subsegmental or subsubsegmental bronchus [3]. This is in contrast to bronchoalveolar lavage (BAL), which samples two sites of infection, i.e., fluid lining the small airways distal to the point of the wedge of the tip of the bronchoscope (alveolar ELF) and alveolar macrophage (AM). BMS is useful for measuring the concentrations of biochemical substances, such as KL-6, albumin, and tumor markers, in bronchial ELF [4, 5]. We have also used this technique to obtain bronchial ELF on the airway surface and determine the time versus concentration profile of levofloxacin, a model antibiotic [6].

Telithromycin belongs to the family of ketolides that are a new class of 14-membered ring macrolides. Telithromycin inhibits protein synthesis by acting mainly on the 50S ribosomal subunit, and it is effective against both common and atypical respiratory tract pathogens [7-12].

The goal of this study was to measure the time versus concentration profile of telithromycin in bronchial ELF sampled by BMS and compare these findings to those found in plasma and alveolar ELF sampled by BAL in non-smoking healthy volunteers after either single or multiple once daily doses for 5 d. In addition, in order to achieve
more information on validation of the BMS method, we compared the concentrations in bronchial ELF at different bronchi at one time point after an oral dose and the concentrations in bronchial ELF of the same bronchus at intervals of at least one month after single or multiple doses.

**Materials and Methods**

**Subjects**

We recruited five healthy volunteers who were non-smokers, 24-25 years old, 42 to 70 kg, and 150 to 175 centimeters tall with no recent lung infections. The institutional ethics committee of Hokkaido University School of Medicine approved the study, and all subjects were provided with detailed descriptions of the study, and written informed consent was obtained from all the subjects.

**Study Protocols**

Each healthy subject was given 600 mg (two 300-mg tablets) of telithromycin (Ketekku; Astellas Pharma Inc., Tokyo, Japan) orally. Bronchoscopy with BMS probe and venipuncture were performed 2, 3, 4, 6, 10 and 24 h later to determine the time versus concentration profiles in both bronchial ELF and plasma. After a washout period of at least 7 d, each subject received 600 mg of telithromycin once daily for 5 consecutive days. Bronchoscopy with BMS probe and venipuncture were performed 0, 2, 3, 4, 6, 10, 24 h after the last dose to determine the time versus concentration profiles in ELF and plasma. After a washout period of at least one month, both BAL and BMS were performed 3 h after a single oral dose of 600 mg telithromycin. Bronchial ELF was obtained at right lower lobe bronchus in the beginning, and next at left lower lobe bronchus, and again at right lower lobe bronchus. Finally, after a wash
out period of at least 7 d, both BAL and BMS were obtained 3 h after treatment with 600 mg telithromycin once daily for 5 consecutive days (Figure1).

BMS under Bronchoscopy

Bronchial ELF sampling was performed with the BMS probe under bronchoscopy [3, 6]. In vitro studies showed that more than 90% recovery could be obtained after 1 mg/l of telithromycin or 2-20 ml of human serum was absorbed to the BMS probe. After each subject received two 300 mg telithromycin tablets, local anesthesia of the upper respiratory tract was achieved using 4% liquid lidocaine. Afterwards, a flexible fiberoptic bronchoscope (BF-1T-200, Olympus, Tokyo, Japan) was inserted into the right lower lobe bronchus. After the working channel of the bronchoscope was flushed with air, the BMS probe (BC-402C, Olympus, Tokyo, Japan), which consisted of a 2.5 mm outer diameter polyethylene sheath and an inner 1.9 mm polyester fiber rod probe attached to a stainless steel guide wire, was inserted through the channel into a subsegmental or subsubsegmental bronchus. The inner probe was advanced slowly into the distal airway and bronchial ELF was sampled by placing the probe gently at a site of targeted bronchial wall for 10 s. The inner probe was withdrawn into the outer sheath, and both devices were withdrawn simultaneously. The wet inner probe was sectioned 2 cm from its tip. Three sectioned probes that were obtained at one time point from each subject were placed in a tared tube and weighed. Two ml of saline were added to the tube, mixed for 1 min, and transferred to a new tube that was stored at -30°C. The probe was then dried and weighed to measure the ELF volume recovered in order to calculate a dilution factor. A blood sample was also collected at the time of bronchoscopy, and the plasma was separated immediately at 4°C at 2,000 g for 15 min and then frozen until assayed for drug concentrations.
A BAL was performed using 200 ml 0.9 % saline divided into four aliquots of 50 ml. The aspirate from the first lavage was discarded to avoid contamination with proximal airway fluids and cells, and the remaining aliquots were pooled for analysis. The lavage was centrifuged immediately at 400 g for 5 min and the supernatant was separated from the cells without delay. Approximately 2 ml of the supernatant was removed so that the urea level in the lavage sample could be measured, and the remainder of the supernatant was used to measure the concentration of telithromycin. The supernatants were frozen at -30°C until the assay. A blood sample was also collected at the time of bronchoscopy, and the plasma and serum were separated immediately at 4°C at 2,000 g for 15 min and then frozen until assayed for drug and urea concentrations, respectively.

Measurement of telithromycin concentrations in plasma and in dilute solution of ELF
Telithromycin concentrations in bronchial ELF, BAL fluid (BALF), and plasma were determined in quadruplicate by a validated agar well method with Micrococcus luteus ATCC9341 as the test organism [13]. Heart infusion agar (HIA; Nissui Pharmaceuticals, Tokyo, Japan) adjusted to pH 9.1-9.2 was used for the plates, which were incubated in air at 35 °C for 24 h. The limit of quantification was 0.002 µg/ml for ELF, BALF, and plasma. Spiked samples were included for quality control and to provide a standard curve. Plasma standards were diluted in antibiotic-free human plasma, and ELF and BALF standards were diluted in phosphate buffer (pH8). Standard curves were prepared with telithromycin concentrations ranging between 0.002 and 2 µg/ml. Best-fit standard curves for the telithromycin assays were obtained.
by linear regression analysis. The intra- and interassay precisions were determined, and the results were considered acceptable when both the inter- and intra-assay differences were less than 15%. Urea concentrations in BALF and plasma were measured according to the method described by Crocker CL [14]. The limit of quantification was 0.05 mg/dl for BALF and plasma.

Since the bronchial ELF sampled by BMS probe was diluted with 2 ml of saline, the concentration of antibiotics in bronchial ELF (ABX$_{br-ELF}$) was determined as follows: ABX$_{br-ELF}$ = ABX$_{BMS}$ x (2 + V$_{br-ELF}$) / V$_{br-ELF}$, where ABX$_{BMS}$ was the measured concentration of antibiotic in the saline-diluted sample, and V$_{br-ELF}$ was the volume of bronchial ELF recovered by the BMS probe [3, 6].

Estimation of the amount of alveolar ELF sampled by BAL was determined by the urea dilution method [15]. Briefly, the estimate volume of alveolar ELF (V$_{ELF}$) was determined as follows: V$_{ELF}$ = V$_{BAL}$ x Urea$_{BAL}$ / Urea$_{serum}$, where V$_{BAL}$ was the aspirated volume of BAL fluid, and Urea$_{BAL}$ and Urea$_{serum}$ were the urea concentration in BAL supernatant and serum, respectively. The concentration of antibiotic in the alveolar ELF (ABX$_{al-ELF}$) was determined as follows: ABX$_{al-ELF}$ = ABX$_{BAL}$ x (Urea$_{serum}$ / Urea$_{BAL}$), where ABX$_{BAL}$ was the measured concentration of antibiotic in BALF.

Statistical Analysis

Paired t test was used to compare the concentrations in plasma and bronchial ELF sampled by BMS. Tukey’s multiple comparison test was used to analyze the concentrations in plasma, bronchial ELF, and alveolar ELF obtained 3 h after telithromycin administration. A $P$ value of $<0.05$ was regarded as statistically significant. The results were presented as means and SD.
Results

No adverse events or clinical complications were observed during the study. The mean ELF volume recovered by the 3 BMS probe for one time measurement was $31.2 \pm 17.0 \text{ µl}$ ($\pm$ SD). Since samples were diluted with 2 ml of saline, the average dilution factor was $91.6 \pm 73.9$.

The concentrations of telithromycin in plasma and bronchial ELF after single (A) and multiple (B) administration plotted against time after the last dose are shown in Figure 2, and the pharmacokinetic data are summarized in Table 1. The mean concentrations of telithromycin in bronchial ELF were greater than those in plasma at all time points after both single and multiple treatments. The mean maximum concentration (Cmax) of telithromycin in bronchial ELF was significantly higher than that in plasma after single administration ($p<0.05$), and showed a tendency towards higher concentration relative to plasma after multiple treatments ($p=0.06$). Times to maximum concentration (Tmax) of telithromycin in plasma and bronchial ELF were $3.0 \pm 0.7$ and $4.2 \pm 1.1$ h after a single dose and $3.2 \pm 0.8$ and $3.6 \pm 1.7$ h after multiple treatments, respectively. The areas under the concentration-time curve from 0 to 24 h (AUC0-24) of telithromycin in plasma and bronchial ELF were $2.86 \pm 0.60$ and $19.5 \pm 10.4$ mg·h/l after single administration and $3.60 \pm 0.49$ and $42.2 \pm 22.7$ mg·h/l after multiple treatments, respectively. The area under the concentration-time curve from 0 to 24 h (AUC0-24) of ELF were significantly higher than those in plasma after single and multiple doses ($p<0.05$). After 5 d of treatment, there was a moderate accumulation of telithromycin in plasma and ELF because AUC values were approximately 1.3-fold and 2.2-fold higher than those after a single dose, respectively.
We compared the antibiotic concentrations from three different bronchial ELF at one time point to confirm the validity of the BMS method. Accordingly, we obtained bronchial ELF at right lower lobe bronchus followed by the left lower lobe bronchus and, finally, the right lower lobe bronchus from four healthy volunteers 3 h after 600 mg of telithromycin. The concentrations in bilateral bronchial ELF and those at right lower lobe bronchus were consistent after repeated sampling (Figure 3A). We also compared the antibiotic concentrations in bronchial ELF of right lower lobe bronchus at two different time points at interval of at least one month 3 h after single (Figure 3B) and multiple (Figure 3C) oral doses of telithromycin, from four and three healthy volunteers, respectively. We also found good agreement between the concentrations measured at intervals of one month after both single and multiple treatments.

Finally, we compared the concentrations in bronchial ELF with alveolar ELF. The mean ± SD aspirated BAL volumes, ELF volumes, total counts of cells recovered from BAL fluid, and the percentage of macrophages were 121.5 ± 17.6 ml, 1.46 ± 0.52 ml, 93.7 x 10^6 ± 31.1 x 10^6 cells per litter, and 78.3 % ± 11.1 %, respectively. The concentration of telithromycin in bronchial ELF was slightly higher than concurrent plasma concentration. In contrast, the telithromycin concentrations in alveolar ELF sampled by BAL were approximately 7 and 12 times higher than concurrent plasma concentration after single and multiple oral doses, respectively (Table 2). After multiple oral administration, the concentrations of telithromycin were significantly greater in alveolar ELF than bronchial ELF and plasma (P < 0.05).

The Cmax and the plasma concentration 24 h after 5 d of treatment with 600 mg telithromycin were 4.66 mg/l and 1.06 mg/l, respectively. The minimum inhibitory concentrations (MIC_{90}), which are the concentrations that inhibits 90% of the isolates for 18 to 24 hours, are 0.5 mg/l, 0.125 mg/l, 4 mg/l, and 0.125 mg/l telithromycin for
**Streptococcus pneumoniae** (including macrolide-lincosamide-streptogramin D-resistant strains), *Staphylococcus aureus, Haemophilus influenzae, and Moraxella catarrhalis*, respectively [16]. Therefore, our data indicates that 600 mg of telithromycin provided adequate ELF levels to maintain therapeutic activity against the above respiratory pathogens, except *Haemophilus influenzae*.

**Discussion**

In the present study, we obtain pharmacokinetic profiles of telithromycin in bronchial ELF from young, healthy, non-smoking subjects after both single and multiple oral administration by BMS method. We previously determined the time versus concentration profile of levofloxacin in the bronchial ELF after single oral administration by BMS method under bronchoscopy. In the present study, we evaluated the validity of this method by comparing bronchial ELF from different bronchi at one time point and the same bronchus after a month interval. Since the antibiotic concentrations in bronchial ELF were very consistent, the BMS method was reasonably validated at least in this situation. In addition, we also determined the time versus concentration profile of antimicrobial agent in the bronchial ELF after multiple treatments using the BMS method.

BAL is an established technique for measuring antibiotic concentrations in ELF of bronchiolo-alveolar regions [2, 15], but it may not be representative of concentration in bronchial regions but in more distal bronchiolar or alveolar regions. In addition, pulmonary disposition studies by BAL collected at a single time per subject does not provide any information on individual Cmax or AUC curve values in ELF. Bronchial mucosal biopsy can also be used for measuring drug concentrations in bronchial
regions; however, the most relevant information concerning the amount of drug in the interstitial fluid and cellular fluid is unknown [17]. While sputum is an easy fluid to obtain, its usefulness is complicated by possible contamination with saliva and blood [2]. Compared with these classical methods, BMS appears to be a reliable method for obtaining bronchial ELF safely, accurately, and repeatedly at multiple time points in one day with minimum contamination. Therefore, it is useful for determining the time versus concentration profile of antimicrobial agents. One limitation with the BMS method is that antimicrobial concentrations in macrophage that represents an important site for intracellular infection can not be measured by the BMS method.

In the present study, telithromycin concentrations were determined by bioassay with Micrococcus luteus ATCC9341 as the test organism [13]. The assay indicates total levels of free and bound telithromycin. The protein binding rates of telithromycin is reportedly 60-70% [18]. Boswell et al. examined the effect of human serum on the in vitro activity of telithromycin and reported that neither the inhibitory nor bactericidal activity of telithromycin was reduced by either 20% or 70% human serum [19]. Therefore, the total drug levels by this assay would give enough information about the efficacy of this drug.

Telithromycin concentrations in bronchial ELF obtained by BMS were significantly lower than those in alveolar ELF obtained by BAL and tended to be higher than plasma 3 h after multiple doses. In addition, the telithromycin concentration in alveolar ELF was approximately 12 times higher than concurrent plasma concentration 3 h after multiple doses. These results are comparable with previous reports [20-22]. In contrast, telithromycin concentrations in bronchial ELF obtained by BMS were greater than those in plasma by 2, 22, and 69-fold at 3, 10, and 24 h after multiple oral doses, respectively, in the present study. Previously, Khair et al.
examined telithromycin concentrations in bronchial mucosa by bronchial biopsy. They showed that the concentrations in bronchial mucosa exceeded those in plasma by 2-fold at 2 h and 6-fold at 12 h and 12-fold at 24 h [20]. Although there are quantitative differences between their study and ours, the penetration patterns to the bronchial regions are similar.

In the present study, single and multiple oral doses of 600 mg of telithromycin provided significantly higher AUC₀₋₂₄ in bronchial ELF compared to plasma. Cmax in bronchial ELF was significantly higher compared to that in plasma after single administration, and showed a tendency towards higher concentration relative to plasma after multiple administration. Since the efficacy of telithromycin depends on concentration rather than time, AUC / MIC and Cmax / MIC ratios are the key parameters for determining efficacy [23]. In addition, population pharmacokinetic analysis performed from clinical data showed that achieving a plasma Cmax / MIC ratio higher than 0.19 was predictive of a good outcome [24]. Since clinical efficacy is more directly related to the drug concentrations at the target site than plasma concentrations, AUC₀₋₂₄ and Cmax of bronchial ELF are more relevant for therapeutic effects than plasma AUC₀₋₂₄ and Cmax. Higher AUC₀₋₂₄ and Cmax in bronchial ELF compared to those in plasma suggest that telithromycin provides adequate ELF levels to maintain activity against respiratory pathogens.

The high penetration of telithromycin into ELF is probably a reflection of its amphipathic structure. A number of in vitro experiments showed that telithromycin was concentrated in macrophages and white blood cells [23]. Therefore, random presence of white blood cells in ELF samples may contribute to variability even in healthy subjects. In addition, white blood cells would be present in much higher extent in ELF of infected patients than in healthy subjects. While this study was conducted on
healthy subjects, it is likely that infections would increase the concentrations of telithromycin in ELF. This is because not only increased blood flow and higher capillary permeability, but also chemotaxis of white blood cells from inflammation will actually increase the rate of penetration of telithromycin into the lung [25,26].

In conclusion, BMS was validated and reconfirmed to be a feasible and reliable method for measuring antimicrobial concentrations in bronchial ELF. In addition, the BMS is useful to study the pharmacokinetics of drugs in respiratory tract after both single and multiple treatments of antimicrobial agents. Since we investigated one drug in a limited population, additional studies using other antimicrobial agents in larger populations are required to make definitive clinical conclusions concerning the utility of the BMS method.
Figure captions

Figure 1.
The study protocol. After five young, healthy, non-smoking subjects received 600 mg of telithromycin orally, bronchoscopy with BMS probe and venipuncture were performed 2, 3, 4, 6, 10 and 24 h later. After a washout period of at least 7 d, each subject received 600 mg of telithromycin once daily for 5 consecutive days, and bronchoscopy with BMS probe and venipuncture were performed 0, 2, 3, 4, 6, 10 and 24 h after the last dose. After a washout period of at least one month, BAL and BMS were performed 3 h after a single oral dose of 600 mg telithromycin. After another washout period of at least 7 d, BAL and BMS were performed 3 hour after 5 consecutive daily doses of 600 mg telithromycin.

Figure 2.
The mean concentration versus time profiles in plasma (open circles) and in bronchial ELF (filled circles) of telithromycin after (A) single oral administration of 600 mg (n = 5) and (B) multiple oral administration of 600 mg once daily for 5 d (n = 5). Data are presented as means ± SEM.

Figure 3.
Validation of the BMS method.
A. The concentrations of telithromycin in bronchial ELF at different bronchi at one time point after a single oral dose. Bronchial ELF was obtained initially at right lower lobe bronchus, and next at left lower lobe bronchus, and finally at right lower lobe bronchus 3 h after single oral administration of 600 mg telithromycin (n=4).
B. The concentrations of telithromycin in bronchial ELF of the same bronchus at
intervals of at least one month after an oral dose of telithromycin. (n=4).

C. The concentrations of telithromycin in bronchial ELF of the same bronchus at intervals of at least one month after multiple doses of telithromycin. (n=3).
Table 1. Key pharmacokinetic parameters of telithromycin in plasma and bronchial ELF after single and multiple oral doses of 600 mg (n=5).

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<th>Single administration</th>
<th>Multiple administration</th>
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<td>Plasma</td>
<td>Bronchial ELF</td>
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<tr>
<td>AUC&lt;sub&gt;0-24&lt;/sub&gt; (mg·h/l)</td>
<td>2.86 ± 0.60</td>
<td>19.5 ± 10.4*</td>
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<tr>
<td>Cmax (mg/l)</td>
<td>0.68 ± 0.24</td>
<td>1.71 ± 0.67*</td>
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<tr>
<td>Tmax (h)</td>
<td>3.0 ± 0.7</td>
<td>4.2 ± 1.1</td>
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AUC<sub>0-24</sub>: area under the concentration-time curve from 0 to 24 h. Cmax: maximum concentration. Tmax: time to maximum concentration. Data are presented as means ± SD. *significant difference vs. plasma (p<0.05).
Table 2. Concentrations of telithromycin in plasma, bronchial ELF, and alveolar ELF 3 hours after single and multiple oral doses of 600 mg (n=5).

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<th>Multiple administration</th>
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<td>Plasma (mg/l)</td>
<td>0.36 ± 0.19 (1)</td>
<td>0.63 ± 0.11 (1)</td>
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<tr>
<td>Bronchial ELF (mg/l)</td>
<td>0.47 ± 0.39 (1.4)</td>
<td>1.67 ± 0.79 (2.8)</td>
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<tr>
<td>Alveolar ELF (mg/l)</td>
<td>2.94 ± 2.64 (7.3)</td>
<td>7.51 ± 4.54 (12.2)*</td>
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Data are mean ± SD. Parentheses indicate fold increase compared to concentration in plasma.

*Following multiple administration, telithromycin concentrations in alveolar ELF were significantly higher than those in plasma and bronchial ELF (P<0.05).
References


Telithromycin administration

Interval of at least 7 days

BMS 2, 3, 4, 6, 10, and 24 hour after administration

BMS 0, 2, 3, 4, 6, 10, and 24 hour after last administration

BMS+BAL 3 hour after administration

BMS+BAL 3 hour after last administration

Interval of at least one month

Interval of at least 7 days