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Assessment of the Period for Administration of Antibiotics for Primary Atypical Pneumonia

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ABSTRACT. We assessed adequate period for administration of antibiotics for primary atypical pneumonia (PAP). The subjects were patients with PAP admitted to our hospital from January, 1986 to December, 1988. For treatment, 100 mg of minocycline (MINO) was dissolved into 100 ml of solution and infused intravenously for 1 hour twice a day. The patients were divided into two treatment periods: a 6 day-administration group (Group A), and a 9 day-administration group (Group B). Group A: 23 cases (which included 8 cases of mycoplasmal pneumonia) and Group B: 22 cases (which included 10 cases of mycoplasmal pneumonia). A comparative assessment was made between Groups A and B regarding body temperature, WBC, erythrocyte sedimentation rate, CRP and chest X-ray on the 3rd, 6th and 9th days of treatment but no significant difference was observed. Residual shadows at the discontinuance of treatment were present in 61% of Group A and in 36% of Group B but they disappeared gradually in both groups. No recurrent cases were observed in either Group A or B within 1 month after treatment was finished.

As for the PAP treatment period using an intravenous drip infusion of minocycline, no significant clinical difference was observed between administration for 6 and 9 days, suggesting that the 6 days administration suffices for treatment. Even though the possible bacterial residue was unknown as no separation of mycoplasma pneumoniae was attempted, there were no recurrent cases.

Key words : primary atypical pneumonia — therapeutic period — minocycline

Chemotherapy for pneumonia has attained remarkable progress owing to the development of various antibacterial drugs. Pneumonia accompanied with severe pulmonary disorder or secondary pneumonia is often intractable and poses difficulties in selecting antibacterial drugs at times, but it is possible to easily cure most cases of primary pneumonia with less difficulty in selecting antibacterial drugs at times. Primary atypical pneumonia (PAP) holds an important position among primary pneumonia as the antibacterial drugs selected for treatment have almost been established.[1] However, there is no clinical report regarding the assessment of the period for administration of antibacterial drugs for primary atypical pneumonia and there is no established rule for the therapeutic period. To set up a suitable therapeutic period, that is, the minimally required period

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of administration, is a very important issue in thinking about the aspects of cost and effectiveness other than side effects.

Herein the authors have reported a clinical study with the purpose of investigating a suitable therapeutic period for PAP.

SUBJECTS AND METHODS

The subjects were 52 patients with PAP admitted to our hospital from January, 1986 to December, 1988. For treatment, 100 mg of minocycline (MINO) was dissolved into a 100 ml solution and infused intravenously for 1 hour twice a day. For the therapeutic period, the patients were divided into a 6 day-administration group (Group A) and a 9 day-administration group (Group B), and classified alternately into Groups A and B in order of admission. The subjects were selected only from those whose treatment with MINO was found to be possible based on the judgement of its effectiveness from pyrexia, leukocyte count, erythrocyte sedimentation rate, CRP and chest X-ray on the 3rd or 4th therapeutic day.

Expansive degree of shadow in chest X-ray was judged according to Miki's classification chest X-ray scoring.[2] This expresses the expansive degree of shadow numerically, from 1 mark which was defined as a very mild shadow remaining within a single intercostal spaces, increasing in proportion to the expansion of the shadow, to 10 marks which was defined as the range of shadow which almost covers the entire bilateral pulmonary region. Student's t-test was used to test significance of difference.

RESULTS

Out of 52 PAP cases, the 45 subjects selected for investigation were divided into Group A (23 cases, with 8 cases of mycoplasmal pneumonia) and Group B (22 cases, with 10 cases of mycoplasmal pneumonia). The dropout cases were as follows : 3 cases for whom treatment was discontinued due to the presence of hepatic disorder, and 4 cases who failed to comply with the designated therapeutic period.

The background factors of the both Groups A and B are shown in Table 1. The ages averaged 34.2 and 35.8 in Groups A and B, respectively, not a significant difference. An underlying disease was found in 6 Group A cases : 3 cases of bronchial asthma and 3 cases of cerebral palsy. The 2 cases of underlying disease in Group B were Down syndrome and cerebral palsy. The period from onset of PAP to commencement of treatment averaged 5.7 days in both Groups A and B.

Comparisons of pyrexia, leukocyte count, erythrocyte sedimentation rate, CRP and chest X-ray used as indices for judgement of therapeutic effect between Groups A and B are shown in Table 2. 20 cases in each group had pyrexia before treatment and average body temperatures were 38.4°C in Group A and 38.3°C in Group B, showing no significant difference. Nor was a significant difference observed between the two groups in leukocyte count, erythrocyte sedimentation rate, CRP and expansive degree of shadow in chest X-ray.

The courses of pyrexia, leukocyte count, erythrocyte sedimentation rate,

TABLE 1. Background factors in Groups A and B

i) Age
Group A : 17-69 (34.2)
Group B : 16-69 (35.8)
ii) Underlying diseases
Group A : Present 6 cases, None 17 cases
Group B : Present 2 cases, None 20 cases
iii) Period from onset to commencement of treatment
Group A : 1-21 days (5.7 days)
Group B : 1-14 days (5.7 days)

TABLE 2. Comparative assessment between Groups A and B before commencement of treatment

	Pyrexia	WBC	ESR (1 hr)	CRP	Chest X-ray*
Group A	38.4°C	6691	52.4	3.8(+)	3.5
Group B	38.3°C	6350	52.0	4.4(+)	4.1
Significant difference	N.S.	N.S.	N.S.	N.S.	N.S.

*Chest X-rays scored by Miki's classification

CRP and chest X-ray used as the indices for judgement of therapeutic effect were comparatively assessed on the 3rd, 6th and 9th therapeutic days. First, the results regarding pyrexia are shown in Table 3-1. Fevers broke with time in both groups, and no significant difference was observed in the mean body temperature values of the pyrexial cases during the therapeutic course, as half the cases in each group recovered the normal temperature on the 3rd therapeutic day. The number of pyrexial cases increased slightly from the 6th to the 9th day in both groups. These were cases in whom slight fevers of 37.1-37.3°C occurred, a transient rise from normal temperature for 1-3 days ; these were, however, not presumed to be due to recrudescence. Next, the results of the indices are shown as follows : leukocyte count in Table 3-2, erythrocyte sedimentation rate in Table 3-3 and CRP in Table 3-4. No index revealed a significant difference between the two groups and each index improved with time. The results of chest X-rays scored by Miki's classification before and

TABLE 3-1. Therapeutic courses in Groups A and B —Pyrexia—

	Before treatment	3rd day	6th day	9th day
Group A	38.4°C (20 cases)	37.6°C (10 cases)	37.2°C (3 cases)	37.1°C (4 cases)
Group B	38.3°C (20 cases)	37.3°C (9 cases)	37.3°C (3 cases)	37.2°C (6 cases)
Significant difference	N.S.	N.S.	N.S.	N.S.

Upper row indicates the means in pyrexial cases. The figures in ( ) are the number of pyrexial cases.

TABLE 3-2. Therapeutic courses in Groups A and B —WBC—

	Before treatment	3rd day	6th day	9th day
Group A	6691	5508	4772	5456
Group B	6350	5150	5518	5500
Significant difference	N.S.	N.S.	N.S.	N.S.

TABLE 3-3. Therapeutic courses in Groups A and B —ESR (1 hr)—

	Before treatment	3rd day	6th day	9th day
Group A	52.9	36.8	25.1	26.7
Group B	52.8	52.0	38.4	24.3
Significant difference	N.S.	N.S.	N.S.	N.S.

TABLE 3-4. Therapeutic courses in Groups A and B —CRP—

	Before treatment	3rd day	6th day	9th day
Group A	3.8	2.0	0.38	0.25
Group B	4.4	2.63	1.27	0.1
Significant difference	N.S.	N.S.	N.S.	N.S.

TABLE 3-5. Therapeutic courses in Groups A and B —Chest X-ray*—

	Before treatment	3rd day	6th day	9th day
Group A	3.5	2.6	1.8	0.9
Group B	4.1	2.7	1.7	0.8
Significant difference	N.S.	N.S.	N.S.	N.S.

* Chest X-rays scored by Miki's classification

TABLE 3-6. Residual pneumonic shadow after discontinuance of treatment

	At discontinuance	7th day	14th day	14th day<	Not judgeable	Recurrent cases
Group A	14 cases	4 cases	0	0	5 cases	0
Group B	8 cases	4 cases	1 case	0	4 cases	0

during treatment are shown in Table 3-5. The shadows reduced with time in both groups, and no significant difference was seen in the degree of improvement during treatment in the comparison made between the two groups. The state of residual shadows after discontinuance of treatment is shown in Table 3-6.

Residual shadows after discontinuance of treatment were seen in 14 out of 23 (61%) Group A cases, on the 6th therapeutic day, and in 8 out of 22 (36%) Group B cases, on the 9th therapeutic day. However, the number of cases with observable shadows decreased sharply to 4 cases in both groups, 7 days after discontinuance of treatment, and only 1 case remained with shadow in Group B on 14th day. However, the shadow in this particular case disappeared rapidly afterwards. The cases where the therapeutic course could not be followed till the shadow disappeared completely were "not judgeable", but the degree of residual shadow in the final chest X-ray in such cases was mostly degree 1 of Miki's classification. No recurrent case was observed within about 1 month after discontinuance of treatment in either Group A or B.

As for side effects in terms of abnormal clinical laboratory values, increases in GPT and GOT were observed in 3 cases out of 52 (5.8%). However, abnormalities in all 3 cases were alleviated rapidly after discontinuance of treatment with MINO.

CASE PRESENTATION

The case was a male aged 12 with mycoplasmal pneumonia, whose clinical course is shown in Fig. 1. Drip intravenous infusion of MINO was commenced at hospitalization, but the presence of a hepatic disorder was found on the 2nd day of treatment. Therefore, treatment with MINO was discontinued after a day and a half and switched to a drip intravenous infusion of erythromycin in 500 mg, which was, however, discontinued due to rash. Subsequently, the patient's course was observed without the use of antibiotics, and pyrexia, CRP and chest X-ray were relieved smoothly. No recurrence was observed for 6 months after treatment.

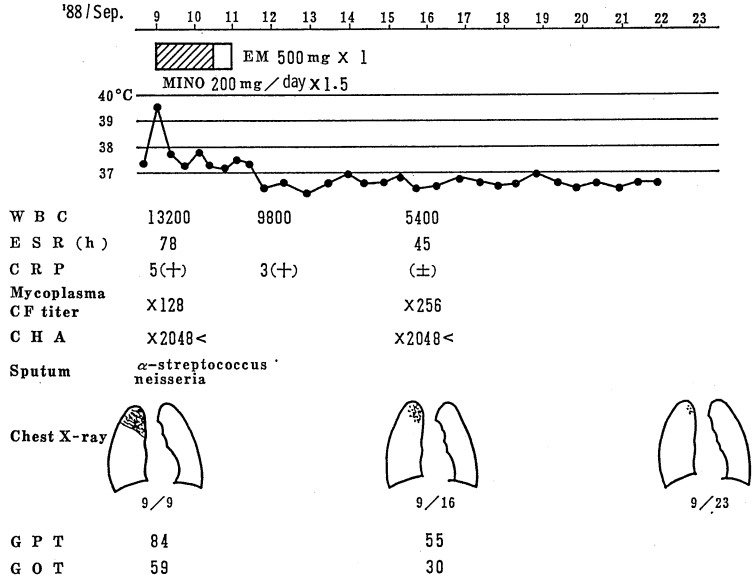

Fig. 1. Case : 12 year-old male, mycoplasmal pneumonia

DISCUSSION

There is consensus of opinion for discontinuance of antibacterial drugs when the administration is judged ineffective and when side effects develop, but there are frequent occasions when we waver in our judgement as to how long the administration should be continued when the treatment is judged to be effective and continuable without side effects. It is difficult to decide on an appropriate time for discontinuing chemotherapy, and there are not many reports which have dealt with this point. Presumably, in the existing circumstances involving pneumonia, treatment is prolonged without any definite idea about the suitable period simply because of an anxiety about a reccurence or recrudescence. However, when an adequate antibacterial drug has been selected, deciding on a suitable period for treatment is considered essential from the aspects of cost and effectiveness.

PAP is the pneumonia we encounter frequently at outpatient clinics, holding an important position among community-acquired pneumonia.[3] In the case of PAP, once thc causative organism such as mycoplasma pneumoniae has been determined, the disease should be titled with the name of the causative organism, for example, as "mycoplasmal pneumonia". Though PAP can not be said to be a strict diagnostic name, such a name is considered to be useful clinically for setting up a rough basis for the selection of antibacterial drugs. The disappearance of the bacteria remaining in the inflammatory region is the most important point when the time for discontinuing the use of an antibacterial drug is discussed. However, no strict differentiation is clinically possible, and we are frequently unable to detect the causative organism particularly in case of pneumonia.[4] Age, an underlying disease or the presence or not of pulmonary injury are considered as factors exerting influence on the therapeutic period for pneumonia. Because many PAPs are moderate or less severe, originate in healthy adults and lack complicated background factors, PAP is an adequate object for studying the therapeutic period.

Oshitani *et al.* propose that a therapeutic period of 3–7 days is a yardstick for the so-called community acquired pneumonias such as mycoplasmal pneumonia or primary pneumonia.[5] It was presumed in the authors' assessment that there were no clinical differences in the periods of treatment by drip intravenous infusion of MINO for PAP between 6 and 9 days, and that PAP is curable by the 6-day treatment. As for mycoplasmal pneumonia, there are reports recommending chemotherapy for a relatively long period, reasoning that a 1 week treatment is insufficient as the discharge of mycoplasma pneumoniae from the lung continues for a comparatively long period even after symptomatic alleviation is attained.[6] However, in our assessment of 18 cases of mycoplasmal pneumonia, no significant difference was observed between the 8 cases in the 6 day-treatment group and the 10 cases in the 9 day-treatment group, suggesting that PAP is curable by a 6 day-treatment. No assessment was made regarding the turning of bacteria to negativity since no attempt was made to isolate mycoplasma pneumoniae. However, the 6 day-treatment did not cause a recurrence or recrudescence in any of the 8 cases. In the case of mycoplasmal pneumonia presented above, treatment was discontinued after 2 days due to hepatic disorder, but the case was cured completely, at least clinically, without a recurrence in the following 6 months observation of the course.

Residual pneumonic shadows at discontinuance of treatment were observed in 61% of the 6 day-treatment group and 36% of the 9 day-treatment group, but the shadows disappeared almost completely in the 14 days after discontinuance of treatment. As a shadow which becomes residual subsequently is presumed to be reduced naturally even if the treatment is discontinued at least in PAP, it is considered incorrect to discontinue antibacterial drug treatment when the pneumonia shadow disappears. Oshitani *et al.* found that a suitable condition for discontinuing treatment with antibacterial drugs is achieved when CRP is less than 2(+), leukocyte count is nearly below 8,000 and the body temperature is normalized in addition to the chest X-ray score being below 3 marks, on the premise that the respective findings take favorable turns.[5)]

As a result, we have been able to clarify that for PAP, a 6-day drip intravenous treatment with MINO is sufficient if this treatment is confirmed to be clinically effective. Further careful assessment is required to confirm if a 6 days duration is an adequate therapeutic period or not, but it is presumed that no prolonged treatment is necessary. The possibility of shortening the therapeutic period further awaits future clarification.

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