CASE 74

Application of Mahalanobis Distance to the Measurement of Drug Efficacy

Abstract: Despite various evaluation methods of drug efficacy designed to date, we do not yet have a single definitive technique. It is widely known that there are few cases in which the data follow a normal distribution; particularly in the clinical field, there is no guarantee that the data follow such a distribution. Moreover, medical data for patients tend to have considerable variability compared with those for healthy people. Also, the number of items to be studied has been increasing as medical science has advanced. If these data are analyzed as raw response data, the reliability of the results calculated is considered to deteriorate. In these contexts we attempted to use a Mahalanobis distance (D^2), which is regarded as a comprehensive judgment, to assess drug efficacy.

1. Introduction

In general, few drugs are effective for chronic hepatitis. Even Interferon, which has lately been said to be a cure for hepatitis C, has only a 40 to 50% efficacy rate. For hepatitis B the rate is believed to be much smaller. Moreover, Interferon causes significantly strong sideeffects, and at the same time, cannot be applied to all patients suffering from hepatitis. In our research we use Azelastine, an antiallergy medicine. We examined two groups: (1) healthy persons and (2) patients with chronic hepatitis.

Healthy Persons (Normal Group)

We examined 200 people, who took a biochemical test consisting of 16 examination items (described later), and from the diagnostic history at Tokyo Teishin Hospital, these people were diagnosed as being in good health with no disease. Although initially, we wished to increase the number of examinees, because of the limited capacity of the computer used at that time, we had to be content with only 200 people.

Patients with Chronic Active Hepatitis

The patients with chronic active hepatitis to be studied were 32 males who had visited the Department of Digestive Systems at Tokyo Teishin Hospital over three years and whose medical checkup data had been stored. The active period of chronic hepatitis does not represent a stable condition but indicates a stage when many liver cells die. Using more popular terminologies, we can view it as a period with high GOT or GPT values (see below).

- *Contrast group.* This group consisted of 16 patients with chronic active hepatitis who had taken an orginary three-year course of therapy. No Interferon had been prescribed for them.
- *Azelastine group.* This group comprised 16 patients with chronic active hepatitis who had been medicated with Azelastine for one year

and who were now in the second year of therapy.

Items Studied

The healthy persons and patients with chronic active hepatitis had already had the following 16 blood tests: total protein (TP), albumin (Alb), A/G (albumin/globulin) ratio, cholinesterase (ChE), glutamate oxaloacetate transaminase (GOT), glutamate pyruvate transaminase (GPT), lactate dehydrogenase (LDH), alkaline phosphatase (ALP), γ-glutamyltranspeptidase (γ-GTP), leucine aminopeptidase (LAP), total cholesterol (TCh), triglyceride (TG), phospholipases (PL), creatinine (Cr), blood urea nitrogen (BUN), and uric acid (UA).

In addition, assuming the age and gender of the examinees to be relevant and that no extra cost was needed for data collection, we added both to the 16 examination items.

Analysis Method

The Mahalanobis distance D^2 was not convenient to analyze as raw data. We divided D^2 by the degrees of freedom, 18. The average of the resulting values for the normal group was equal to 1. Next, by logarithmizing the value above and multiplying it by 10, we obtained the value used in our analysis. Then the data for the ith patient were computed as follows:

$$Y_i = 10 \log \frac{D_i^2}{18}$$

This value is called a *decibel value*.

Table 1
Data for normal group

Age:	No. 1 59 Male	No. 2 51 Female	No. 3 38 Male	No. 4 56 Female
TP (g/dL)	6.5	7.0	7.1	7.2
Alb (g/dL)	3.7	4.4	4.3	4.0
A/G	1.32	1.69	1.54	1.25
ChE (ΔpH)	0.70	0.98	0.92	0.93
GOT (IU/L)	12	21	16	22
GPT (IU/L)	6	18	15	16
LDH (GU/dL)	190	247	152	188
ALP (KAU/dL)	7.7	6.3	4.8	6.1
γ-GTP (IU/L)	12	23	40	16
LAP (U/dL)	275	340	355	304
TCh (mg/dL)	235	225	177	216
TG (mg/dL)	140	87	93	86
PL (mg/dL)	238	227	185	213
Cr (mg/dL)	0.8	1.1	1.4	1.0
BUN (mg/dL)	1.3	15	15	13
UA (mg/dL)	3.8	4.6	4.6	4.2

2. Analysis Results

From here on, we detail the actual data and analysis results.

Data for the Normal Group

Table 1 shows a part of the data for 200 healthy persons.

Data for Patients with Chronic Active Hepatitis

Since the total data for patients with chronic active hepatitis were composed of 32 examinees, 36 months, and 18 items, we show only a part of them in Table 2.

Mahalanobis Distance

Since D^2 for the normal group comprises variances with 18 degrees of freedom and is considered relatively small, we do not show the actual data here. For the contrast and Azelastine groups for chronic active hepatitis, we show a part of the data of D^2 in Table 3. however.

Performing an analysis of variance for the decibel values (Y's) and calculating the estimations us-

Table 2
Data for patients with chronic active hepatitis[a]

	1 M	2 M	3 M	4 M
TP (mg/dL)	7.0	7.9	7.9	7.8
Alb (mg/dL)	3.6	4.0	3.6	4.1
A/G	1.06	1.03	0.97	1.08
ChE (IU/L)	303	275	312	297
GOT (IU/L)	178	168	160	174
GPT (IU/L)	225	228	218	202
LDH (IU/L)	446	429	454	467
ALP (IU/L)	152	146	146	162
γ-GTP (IU/L)	27	31	28	30
LAP (IU/dL)	59	69	64	68
TCh (mg/dL)	186	185	181	197
TG (mg/dL)	153	148	100	157
PL (mg/dL)	193	222	198	216
Cr (mg/dL)	0.7	0.7	0.7	0.7
BUN (mg/dL)	11	12	11	15
UA (mg/dL)	5.9	0.7	5.6	5.5

[a] Case 17 in Azelastine group: 47-year-old male.

Table 3
Mahalanobis distance for patients with chronic active hepatitis

Item	No. 17	No. 18	No. 19	No. 20
1	1554.0	1873.6	1216.5	1418.6
2	1741.7	2869.2	2550.1	1164.8
3	1531.9	1412.8	1190.5	1239.7
4	1248.8	1877.5	1656.3	903.1
5	1871.2	1756.8	2558.0	533.3
6	1362.9	1881.7	2100.2	896.3
7	2346.0	2346.3	2808.8	623.7
8	2489.1	1195.0	2207.3	710.8
9	2492.7	790.5	1843.8	790.3
10	3380.7	990.1	367.7	918.0
11	3196.8	1416.1	1784.8	862.9
12	2815.7	1301.7	2398.7	811.8
13	2191.2	131.2	473.6	739.5
14	2218.3	979.4	204.1	690.8
15	1930.3	1306.5	560.2	884.2
16	1787.3	1662.5	157.2	332.8
17	2572.1	1348.3	178.1	393.9
18	1893.3	1650.7	498.1	604.6
19	1298.3	1223.9	738.0	520.2
20	1508.3	1329.2	948.3	969.2
21	1634.1	1180.4	1175.2	274.6
22	1785.5	1106.5	942.8	339.6
23	1546.5	560.4	366.6	269.9
24	1284.4	782.4	1049.5	56.6
25	2037.8	1286.7	1652.9	59.2
26	2294.8	588.8	432.9	84.1

ing them, we arrived at Figure 1. For the sake of simplicity, we do not indicate the 95% confidence limits.

Looking at Figure 1, we can see that the Azelastine group shows a greater distance from the normal group than the contrast group does. Considered not so good as a comparative test of group 2, this fact is likely to reflect the effects of a special drug on patients with poor values in the clinical test or with serious conditions.

In addition, for both the contrast and Azelastine groups, the Mahalanobis distance is on the increase in the first year. However, for the second year, the distance is on a downward trend, due partly to the effect of more active therapy. One of the most remarkable changes is that the Azelastine group's distance ends at approximately the same place as that of the contrast group.

In the third year, although the contrast group's distance increases temporarily, it tends to return back to the initial state. In contrast, for the Azelastine group, the distance continues to decline and finally assimilates with that of the contrast groups.

Judgment by the Linear Trend

We notice no relationship among all data on the whole. Although various types of analysis methods have been attempted to date, we detail the linear trend analysis as a typical example.

Table 4 shows the average of each case, the corresponding value of the linear equation, and the value that we obtain by dividing it by the total of squares of coefficients (which is equivalent to a monthly slope for the linear trend). Performing an analysis of variance for these linear trend values, we obtain Table 5. Based on this result, we calculated the estimations shown in Table 6. From these we can conclude that since a Mahalanobis distance is considered a distance from the gravity center of a multidimensional space, if the distance for a certain patient from the normal group increases, the degree of his or her disease is regarded to increase. On the contrary, as the distance decreases, the patient becomes better and closer to the state of a normal person. As a whole, as compared with the contrast group for chronic active patients, the Azelastine group obviously has a good linear trend. However, this trend does not necessarily hold true for all patients. Yet if we look at the values beyond the 95% confidence limits, the values of the linear trend reveals that the patients are getting better. For example, for the linear trend for the contrast group, the average is -19.9572 and the 95% confidence interval is -202.137 ± 162.2232. On the other hand, the average for the Azelastine group is -115.5413 and its confidence interval is -297.7217 ± 66.6391. Therefore, patients 17, 19, 20, and 32, those who take the linear trend value below the 95% confidence interval, are judged to be getting

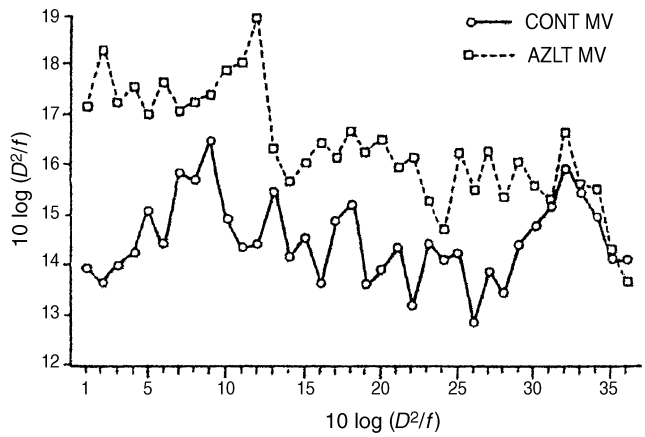

Figure 1
Plots for contrast and Azelastine groups

Table 4
Linear trend of 10 log(D^2/f) (for one month)

Contrast Group			Azelastine Group		
CN	***L***	***L/D***	**CN**	***L***	***L/D***
1	−58.3	−0.0065	17	−419.8	−0.0470
2	+51.3	+0.0057	18	−121.8	−0.0136
3	−67.9	−0.0076	19	−249.0	−0.0279
4	+87.7	+0.0098	20	−289.6	−0.0324
5	−116.4	−0.0130	21	−189.8	−0.0213
6	−46.9	−0.0053	22	−123.5	−0.0138
7	−27.1	−0.0030	23	−82.5	−0.0092
8	+69.2	+0.0078	24	−185.7	−0.0208
9	−68.6	−0.0077	25	−48.9	−0.0055
10	+48.2	+0.0054	26	+160.5	+0.0180
11	+33.9	−0.0038	27	−22.3	−0.0025
12	−144.45	−0.0162	28	−27.2	−0.0030
13	+122.0	−0.0137	29	+75.5	+0.0085
14	−182.8	−0.0205	30	−72.3	−0.0081
15	−2.1	−0.0002	31	−48.8	−0.0055
16	−17.1	−0.0019	32	−203.5	−0.0228

healthy. In addition, in the Azelastine group, there is no patient whose disease is aggravated with a value beyond the 95% confidence interval of the contrast group. Furthermore, in the Azelastine group, there is no one with a value below the 95% confidence interval of the contrast group. When di-

Table 5
ANOVA for linear trend (L)

Source	f	S	V	F_0
L	1	146,878.7	146,878.7	19.87**
C	1	73,090.5	73,090.5	9.89**
Within C_1	15	110,878.7	7,391.9	
Within C_2	15	300,000.6	20,000.0	2.71*
Total	32	630,848.5		

Table 6
Estimations of linear trend and that divided by D and 95% confidence limit

	L	***L/D***
Contrast group		
Lower limit	−202.1376	−0.022646
Estimation	−19.9572	−0.002236
Upper limit	+162.2232	+0.018174
Azelastine group		
Lower limit	−297.7217	−0.033354
Estimation	−115.5413	−0.012944
Upper limit	+66.6391	+0.007466
Average		
Lower limit	−242.8962	−0.027212
Estimation	−67.7492	−0.007590
Upper limit	−107.3977	+0.012032

viding the value above by the number of units (total of squares of coefficients), the result is completely similar, even in terms of F_0 for an analysis of variance.

3. Conclusions

As a result of comparing an Azelastine-based therapy with common therapies on patients with chronic active hepatitis by taking advantage of the Mahalanobis distance, we conclude that the Azelastine group obviously has a better trend health than that of the contrast group. However, looking at individual patient data, no distinct relationship can be seen. As a final judgment, we conclude that Azelastine can contribute quite effectively to treatment of many patients with chronic active hepatitis.

Reference

Tatsuji Kanetaka, 1992. Application of Mahalanobis distance to measurement of drug efficiency. *Standardization and Quality Control*, Vol. 45, No. 10, pp. 40–44.

This case study is contributed by Tatsuji Kanetaka.