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Blood Concentrations of Amitriptyline-Nortriptyline and Clinical Response in Depressive Patients

Shosuke WATANABE, Shigeo YOKOYAMA, Yutaka ASANO* and Itaru YAMASHITA*

Department of Psychiatry, Kawasaki Medical School, Kurashiki 701-01, Japan
**Department of Psychiatry and Neurology, Hokkaido University School of Medicine, Sapporo 060, Japan*
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ABSTRACT In conducting the double-blind controlled study of antidepressant, observations were carried out on the relationship between the therapeutic effect of amitriptyline and blood ATP, NTP concentrations of 17 patients given ATP as the standard drug. The results may briefly summarized as follows.

1. The blood concentration of the ATP-effective group (markedly effective+effective, N=13) was significantly ($P<0.01$) lower than that of the noneffective group (slightly effective+noneffective, N=4). There could be seen no significant differences of NTP and ATP+NTP concentrations between two groups.
2. The high blood ATP concentration group (over 26 ng/ml) showed higher tendency ($P<0.1$) Hamilton and Beck scores than the low concentration group (under 26 ng/ml).
3. There was an inverse correlationship between the improvement rate (the decrease rate of Hamilton score) and the blood ATP concentration ($= 1.531$, $P<0.05$)
4. There was observed a mutual relationship in the dosage of ATP, the blood concentrations of ATP, NTP, ATP+NTP.
5. A discussion was made on the relationship of blood ATP, NTP concentration to their therapeutic effect.

With the depressive patients we conducted the multi-center double blind controlled study[1] in which the effects and frequency of side effects of maprotiline (MAP) and amitriptyline (ATP) were investigated. Concerning MAP a report[2] was already made about the correlative tendency between the blood concentration and the therapeutic effect.

In the present study using 18 blood specimens obtained from ATP-administered patients in the same study, the relation between the ATP dosage and clinical effect was investigated by measuring the blood concentration of ATP and nortriptyline (NTP).

The report on the correlation between the blood concentration and therapeutic effect of tricyclic antidepressants had its beginning with the study on

渡辺昌祐，横山茂生，浅野裕，山下格

TABLE 1. Backgrounds of patients, amitriptyline dosages and blood levels

Patient No.	Age	Sex	Body Weight	Blood Letting (Weeks Later)	Dosages (mg) Week 1	Week 2	Week 3	Total Doses Before B.L.	Mean Daily Doses (mg/day)	Mean Daily Doses (mg/kg/day)	Before Administration	At Blood Letting	Changes (%)	Hamilton Score	Clinical Effective At B.L.	Concomitant Drugs	Blood Levels ATP (ng/ml)	NTP (ng/ml)	Total (ng/ml)	Remarks
005	30	M	52.0	4	700	875	1050	2625	125.0	2.40	25	12	52.0	+	Sebelase Pantosin NZP 10mg		57	22	79	
011	25	M	55.0	3	525	525	525	1575	75.0	1.36	29	8	72.4	++	NZP 5mg		5	12	17	
022	40	F	49.0	3	350	350	400	1100	52.4	1.07	25	7	72.0	+++	-		13	tr	13	
042	29	M	57.0	3	525	525	1050	2100	100.0	1.75	13	4	69.2	++	NZP 3.3mg		13	9	22	
046	30	F	40.0	3	825	1050	1050	2925	139.3	3.48	23	4	82.6	+++	NZP 10mg		31	6	37	
055	31	M	50.0	3	600	1050	900	2550	121.4	2.43	27	6	77.8	++	Pursenid NZP 10mg		40	44	84	
060	35	F	48.0	3	825	1050	1050	2925	139.3	2.90	33	5	84.8	+++	Effortil Pursenid NZP 12.1mg		31	33	64	
062	49	M	53.0	2	825	1050	(1050)	1875	133.9	2.53	22	13	40.9	++	Actinomycin Pursenid NZP 10mg		46	95	141	
066	63	M	60.0	2	525	700	(700)	1225	87.5	1.46	18	16	11.1	+	Pursenid NZP 5mg		54	10	64	
067	45	M	56.0	2	525	700	(700)	1225	87.5	1.56	21	10	52.4	++	-		4	tr	4	
101	36	F	56.0	2	525	525	(525)	1050	75.0	1.34	24	5	79.2	+++	NZP 10mg		5	10	15	
109	54	F	52.0	3	825	1050	1050	2925	139.3	2.68	41	34	17.1	-	NZP 10mg		48	tr	48	
110	50	M	72.0	3	525	525	1050	2100	100.0	1.39	36	13	63.9	++	NZP 10mg		tr	tr	0	Excluded from Analysis
112	65	F	47.5	3	525	525	525	1575	75.0	1.58	18	2	88.9	+++	-		4	tr	4	
113	21	F	66.0	3	1050	525	525	2100	100.0	1.52	24	3	87.5	+++	NZP 6.7mg		20	0	20	
114	26	M	62.0	3	525	525	525	1575	75.0	1.21	7	1	85.7	+++	-		13	tr	13	
116	47	F	45.0	3	525	525	525	1575	75.0	1.67	32	0	100.0	+++	NZP 10mg		27	3	30	
117	64	M	43.5	2	525	525	-	1050	75.0	1.72	35	33	5.7	-	NZP 10mg		29	0	29	

imipramine by Hyadu et al.[3] in 1962, since then the studies in this field are gradually increasing. In Japan there are only few reports by Tanimukai[4] and Asano[5,6], and even now an integrated data from several sources are required.

SUBJECTS AND METHODS

As reported previously in the multi-center double blind controlled study of an antidepressant effect of MAP using ATP as the standard drug out of 86 patients suffering from various types of depression 45 blood specimens were aspirated in the second or the third week for the measurements of drug concentration in blood there were 26 specimens from the patients receiving ATP, but excluding 8 specimens became impossible due to breakage of test-tubes 18 specimens sewed for the present investigation.

For the blood aspiration, out-patients were asked to come without taking the drug in the morning, and with in-patients 10 ml of blood was aspirated from the elbow vein with a heparinized syringe in the early morning hours before breakfast. The whole blood was stored at -60°C as soon as possible. The extraction of drug was done by the mothod of Curry et al.[7] and for measuring the drug gas chromatographic method[5,6] was employed. By this method the retention time of ATP, NTP, and promazine (an internal standard substance) was 2.23 min, 3.15 min, and 4.85 min respectively. The recovery rate was 98%.

RESULTS

For the 18 patients studied, Table 1 gives the age, sex, body weight, time of sample collection, the dose of ATP, Hamilton score, Beck score and the therapeutic effects at the time of sampling of blood, dosage of drugs, concomitant drugs and ATP and NTP concentrations in blood are also shown in Table 1. The case No. 110 was the one who showed only traces of ATP and NTP in blood, despite receiving 100 mg/day of ATP was considered to have had the poor compliance so that it was excluded from the subsequent analysis.

TABLE 2. Clinical effects and blood levels

$\bar{X}\pm$S.E.

	Slightly Effective + Ineffective n=4	Remarkably Effective + Effective n=13	Test on Significant Differences
Amitriptyline	47.0±6.3	19.4±4.0	$p<0.01$
Nortriptyline	8.0±5.2	16.3±7.6	N. S.
Amitriptyline + Nortriptyline	55.0±10.7	35.7±10.9	N. S.

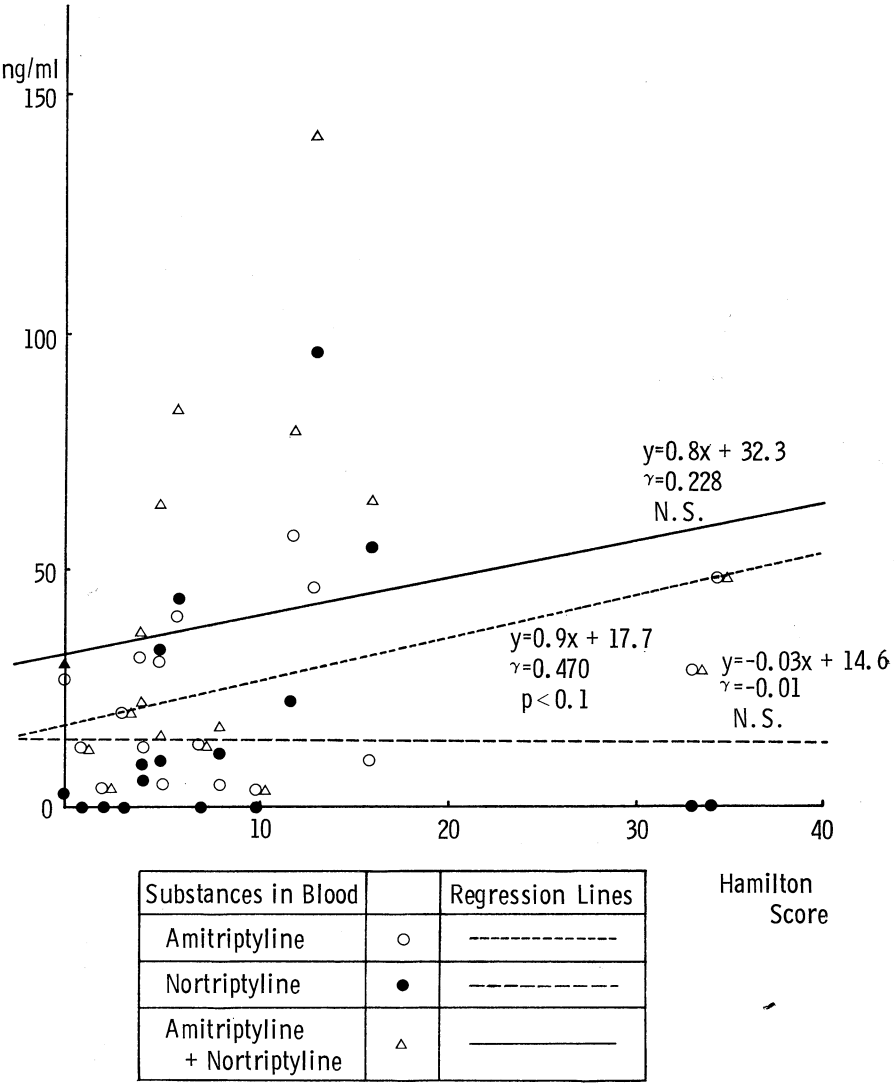


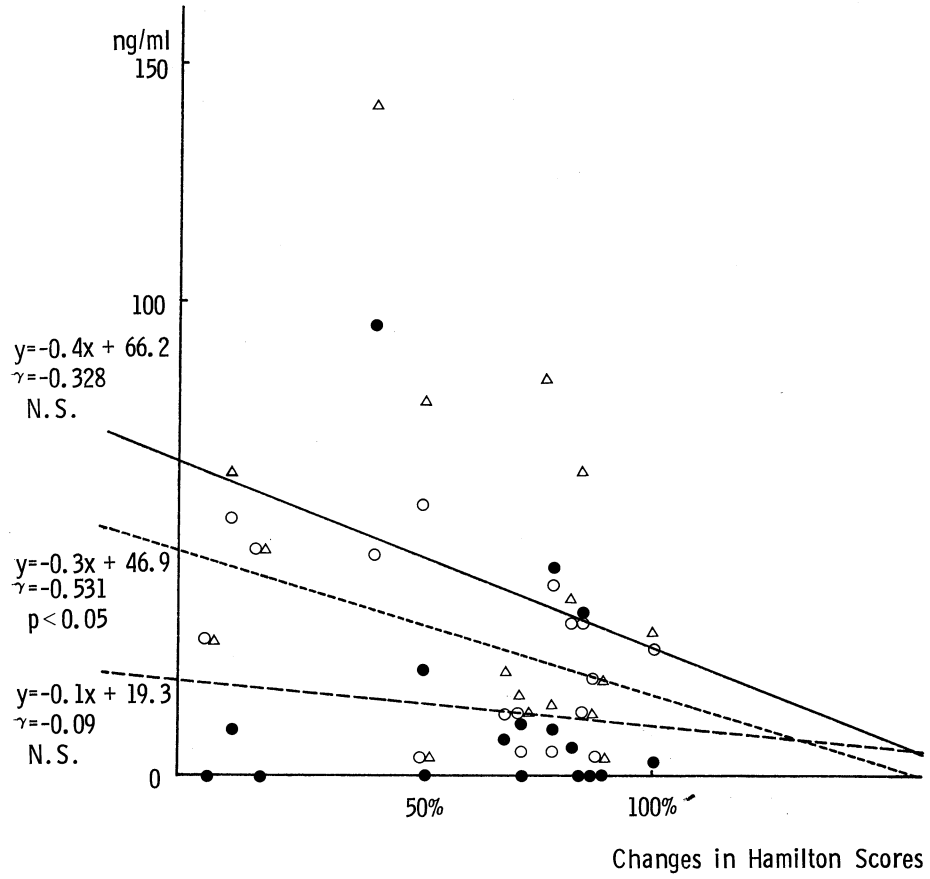
Fig 1. Correlations between Hamilton scores and blood levels

1. The blood concentration and the therapeutic effects of ATP, NTP (Table 2)

The blood concentration of ATP in the therapy-effective group (marked effective+effective) composed of 13 cases was significantly ($P<0.01$) lower than that in the non-effective group (slightly effective and non-effective) of 4 cases. The blood NTP concentration and the ATP+NTP concentration both showed no significant difference between the two groups.

2. The severity of depressive symptom by Hamilton score and the blood concentration of drugs (Fig. 1)

By plotting the Hamilton score on the abscissa and the blood concentration on the ordinate, the regression straight line was drawn (Fig. 1). As a result it was found that by (blood concentration of ATP) equals $0.9 \times$(Hamilton score)



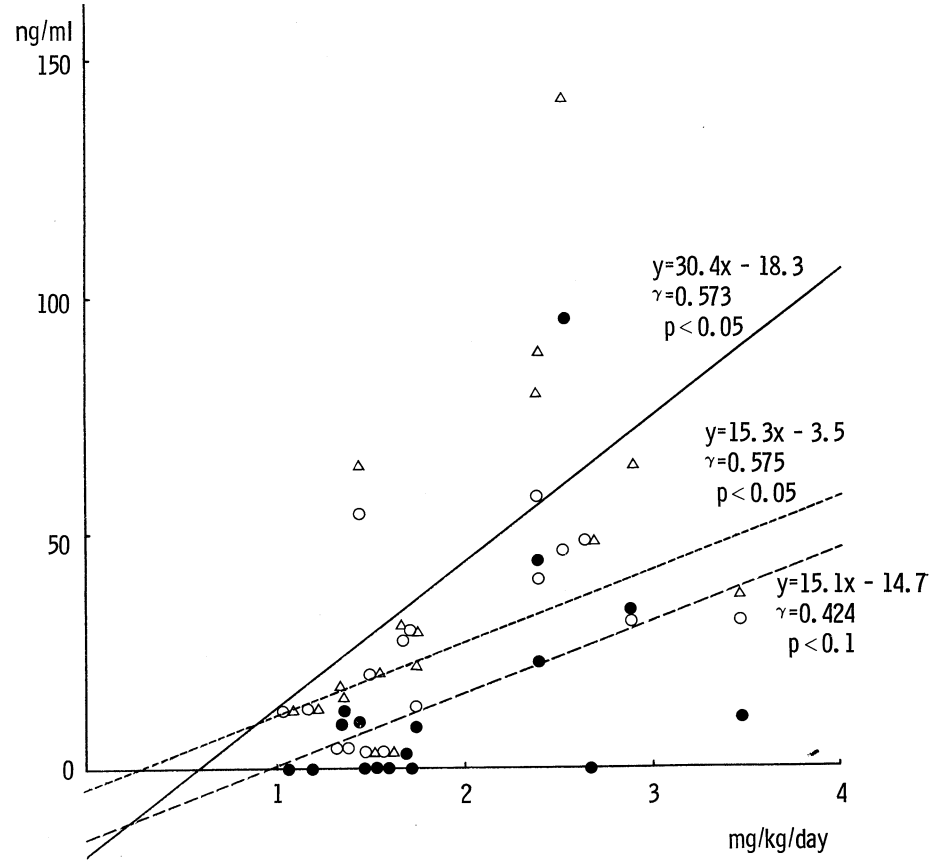
Substances in Blood		Regression Lines
Amitriptyline	○	----------
Nortriptyline	●	---------
Amitriptyline + Nortriptyline	△	————

Fig 2. Correlations between blood levels and % changes in Hamilton scores

+17.7, r=0.47, P<0.1, showing a mutual tendence between the two. Namely, ATP blood concentration tended to be higher in the case where Hamilton score was greater. There could be observed no mutual relationship between the concentrations of NTP as well as ATP+NTP on one hand and Hamilton score on the other.

3. Correlation between the recovery rate of symptoms and blood concentration (Fig. 2)

By dividing the difference between Hamilton score at the initial examination



Substances in Blood		Regression Lines
Amitriptyline	○	----------
Nortriptyline	●	———————
Amitriptyline + Nortriptyline	△	————————

Fig 3. Amitriptyline dosages (mg/kg/day) and blood levels

TABLE 3. Dosage, plasma levels and clinical response of amitriptyline, nortriptyline

Author	Reference No.	Dosage	Plasma levels	Results and Conclusions
Amitriptyline				
Braithwaite et al. (1972)	8	150 mg/day	NTP 20–278 ng/ml ATP 20–227	Significant correlation between plasma level and clinical response, poor response <120 ng/ml
Montgomery et al. (1975)	17	150 mg/day	137±60.2 ng/ml (total)	Better response in 137±60.2 ng/ml than above or below
Ziegler et al. (1976)	22	50–150 mg/day	52–318 ng/ml (total)	Positive correlation between clinical response and ATP+NTP ($P<0.01$), ATP ($P<0.005$) but not NTP Better therapeutic response in 95–250 ng/ml
Kupfer et al. (1977)	15	50–200 mg/day		Positive correlation between clinical improvement and ATP+NTP, ATP, NTP Better response over 200 ng/ml
Ziegler et al. (1977)	24	mean 119 mg/day	ATP+NTP=120 ng/ml	Negative correlation between Hamilton score and ATP+NTP ($\gamma=-0.54$, $P<0.025$) Better response in range 95~200ng/ml
Nortriptyline				
Åsberg et al. (1971)	3	75–225 mg/day	32–164 ng/ml	Curvilineal relationship between in range 50-140 ng/ml
Burrows et al. (1972)	4	150 mg/day	24–592 ng/ml mean 171±19	No simple relationship between plasma level and clinical response
Kragh-Sϕrensen et al. (1973)	12	150 mg/day	48–238 ng/ml mean 141±48.2	Best effect below 175 ng/ml
Burrows et al. (1974)	5	Doses adjusted for required plasma levels	Each pair, one>140 ng/ml, one<49 ng/ml	No correlation, no statistical significant difference between high and low groups
Kraph-Sϕrensen et al. (1974)	13	Doses adjusted for required plasma levels	Each pair, one<150 ng/ml, one>180 ng/ml	High plasma level decreases therapeutic effect Better clinical response in range 50–150 ng/ml
Lyle et al. (1974)	16	35-200 mg/day	44–305 ng/ml	No signfiicant correlation between plasma level and clinical response
Ziegler et al. (1976)	23	150 mg/day	mean 138 ng/ml	Positive correlation between Hamilton score and plasma level ($P<0.01$) Better response in range 50–140 ng/ml than above
Ziegler et al. (1977)	24	mean 117 mg/day	mean 141 ng/ml	Positive correlation between Hamilton score and clinical response ($\gamma=0.49$, $P<0.025$)

and the score at the time of the blood aspiration by the initial score, and this quotient, taken as the recovery rate, was plotted on the abscissa, and by plotting the blood concentration on the ordinate and the recurrent straight line was drawn.

The result showed that in the case of ATP, y(blood concentration of ATP) = -0.3x(the recovery rate)+46.9, r= -0.531 and <0.05, indicating an inverse correlation between the two, but there could be seen no significant correlation between the concentrations of NTP as well as ATP+NTP on one hand and the recovery rate on the other.

4. Correlation between the ATP dosage and the blood concentrations of ATP, NTP, ATP+NTP (Fig. 3)

By representing the dosage of ATP in terms of mg/kg/day (Fig. 3) and its correlation to the blood concentration of ATP, NTP, and ATP+NTP was calculated. As a result there was observed a significant correlation between the dosage and the blood concentration of these substances. Even when the dosage was expressed in terms of mg/day, there could be seen a high correlation between the dosage and the blood concentration.

DISCUSSION

From the present study there was observed a correlation between the blood ATP concentration and its therapeutic effect stated in the following. Namely, the general evaluation 3 weeks after the treatment in the effective group showed a significant low level of ATP concentration ($P<0.01$) as compared to the non-effective group, and there was observed a correlative tendence between Hamilton score and blood ATP concentration ($P<0.1$) within 3 week treatment. Moreover, there was seen an inverse correlation between depression-improvement rate (decrease rate of Hamilton score) and blood ATP concentration and the therapeutic effect are in an inverse correlationship. On the other hand, there can be observed not only definitive relationship between the blood NTP or ATP +NTP concentration and the therapeutic effect.

As to the relation between the blood concentration of tricyclic antidepressant and its therapeutic effect Hyadu[3] first reported in 1962 about 8 depressive patients to whom 150 mg/day of imipramine was given and stated that the blood concentrations in the four responders weve significantly lower than that in nonresponders. Since then the reports concerning ATP and/or NTP concentration and therapeutic effects increased to more than ten add numbers, and these are summarized in Table 3. In these reports there are some who condense that there is a correlation between the blood concentration of the tricyclic antidepressant and its therapeutic effect while others who denied such a correlation, so that there is as yet no integrated opinion. Regarding this there are only a few reports in Japan as those by Tanimukai[4] and Asano[5,6].

As for the study on ATP, Brainthwaite et al.[8] measured the blood concentration (ATP, NTP) in depressive patients 6 weeks after the administration

of 150 mg/day of ATP. They found a great individual difference in the blood concentrations in as a wide range as from 20 - 227 ng/ml ATP and 20 - 278 ng/ml ATP, but they observed a positive correlation between the total concentration of both and the clinical effect, and stated that poor therapeutic effects in the cases receiving less than the total concentration of 120 ng/ml. Gruvstad[9], after re-evaluating these date, stated that the therapeutic effects in the patients receiving the dosage in the range of 70-180 ng/ml are superior. Montgomery[10] administered 150 mg/day of ATP to 28 cases of endogenous depression and found that the therapeutic effects in the cases showing the ATP+NTP concentration in blood within the range of 137+60.2 ng/ml was better than in those cases receiving over or below that concentration. Kupfer et al.[11] reported that therapeutic effect can be attained in the cases receiving ATP+NTP in the concentration of over 200 ng/ml.

Ziegler et al.[12] stated that blood ATP+NTP concentration in the patients administered 150 mg/day of ATP ranges from 0 to 250 ng/ml, showing great individual differences, but Hamilton score and ATP + NTP concentration, ($P<0.001$) as well as ATP concentration ($P<0.05$) showed a mutual correlation, while Hamilton score does not show the mutual correlation to NTP concentration, and further stated that the ATP+NTP concentration which would give favorable therapeutic results will be in the range of 95 - 200 ng/ml.

As such in the treatment with ATP most prevalent opinions state that when the ATP and/or ATP+NTP concentration in blood in the patients is maintained in the range (generally 100 - 200ng/ml) would field favorable results[10,11,13,14]. As for the study of NTP Åsberg and Kragh-Sresen et al.[15–17] state that between the blood concentration and the therapeutic effect there is a curvilinear relationship, and that generally 50 - 150 ng/ml is the effective therapeutic concentration, and in case the concentration above or below that level therapeutic effect would be poor. Whereas there are reports by Australian groups of Burrows et al.[18–21], Lyle et al., stating that there is no mutual relationship between the NTP blood concentration and therapeutic effect. Burrows et al.[18] have clarified that the blood NTP concentration and the clinical effect have no correlationship but there is a correlationship between the dosage of NTP and the blood concentration. They[19,20] further compared the clinical responses in the high concentration group of over 140 ng/ml NTP and the low concentration group of under 50 ng/ml, but there was no significant difference between the two groups. Lyle et al.[22] did not find any correlationship between the blood NTP concentration and clinical response in the patients given 35-200 mg/day of NTP. Ziegler et al.[14,23], however, state that the NTP blood concentration and Hamilton score are correlated ($P<0.001$), i.e. as ATP concentration is in a high range as 150 ng/ml→250 ng/ml the therapeutic effect declines so that it is desirable to keep the therapeuic concentration in the range of 50-140 mg/ml.

On comparing the above reports with the present study, the dosage of ATP ranged 50 - 150 mg/day, average being 49 mg/day which is lower than

theirs. In their reports they give the blood plasma concentration while ours is the whole blood concentration so that it is not comparable in true sense of the word, but it may be worthy of notice that in estimating the plasma concentration by using Ht value, blood ATP or NTP of the ATP+NTP concentration is lower than the concentration reported in Europe and U.S.A. In addition, even in the different concentration group the effective rate of the therapeutic effect in our subjects was as effective as 77% (13/17 cases), indicating that with Japanese patients the concentration much lower than that in Europe and America would be effective. This problem requires further studies.

Next comes a problem how we can interpret the fact that the changing rate of Hamilton score in our study has had an inverse correlationship with the blood ATP concentration. As stated already, Ziegler et al.[23] also reported about NTP in the same sense, but most observations suggest a curviliner relationship between the blood concentration and the therapeutic effect. They state that if the concentration (over 200 ng/ml with ATP, over 150 ng/ml with NTP) rises over a certain limit, the therapeutic effect deminishes.

In our observations therapeutic effect can be obtained even by a small dosage of antidepressant, and the blood concentration also remained at a low level, but the average ATP+NTP concentration obtained from our ATP-nonresponders was 55 ng/ml which was already above the upper limit of the therapeutic concentration, so that it can be understood that the blood concentration of the drug, and the therapeutic effect have come to show an inverse correlationship. In order to further clarify this point it seems necessary to the elucidation conduct of the relationship between the tricyclic antidepressant blood concentration and therapeutic effect by the comparative study on large, better controlled group, and to find out what blood concentration of the tricyclic antidepressant can be used in the actual clinical practive.

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