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Imipramine: Clinical Effects and Pharmacokinetic Variability

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Abstract. Sixty-six hospitalized depressed patients were treated for 4 weeks with imipramine (Tofranil®) 225 mg/day. Blood samples were drawn twice weekly 15 h after the last drug intake, and IP and DMI concentrations in plasma were assayed by quantitative in situ thin-layer chromatography. Clinical rating was carried out once weekly by Hamilton's Rating Scale (HRS), Beck's Depression Inventory, WHO Depression Scale (Quantitative Part), and a side-effect scale. The patients were classified on the basis of the WHO Depression Scale (Qualitative Part) as 'endogenous' ($N = 37$) or 'non-endogenous' depressions ($N = 29$). Antidepressive effect was evaluated on the basis of the posttreatment rating scores.

In patients classified as 'endogenous' depressions all 12 responding patients (HRS $\leqq 7$) had plasma levels of IP > 45 µg/l and DMI > 75 µg/l, whereas 11 out of 14 nonresponding patients (HRS $\geqq 16$) had plasma levels of one or both compounds below these limits. Ten out of 12 responders had levels of IP + DMI above 240 µg/l, and all nonresponders had levels of IP + DMI below this limit. Patients with partial response (HRS: 8–15) formed an overlapping group. There was no sign of an upper plasma level limit for the antidepressive effect of imipramine.

The plasma level/effect relationship was less clear in patients with 'non-endogenous' depressions, since several of them responded at low plasma levels.

Some relationship between effect on blood pressure (orthostatic effect) and high plasma levels of IP and DMI was found.

Using a plasma level limit of IP $\gtrless 45$ µg/l and DMI $\gtrless 75$ µg/l, it was possible to predict the response of the 'endogenous' depression group for 10 out of 12 responders and 10 out of 14 nonresponders on the basis of plasma level measurements obtained after 1 week of treatment.

Key words: Endogenous/non-endogenous depressions – Imipramine – Desipramine – Plasma levels – Rating scales – Clinical effect – Side effects – Therapy control

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With the introduction of sensitive, specific, and reproducible methods for analysis of the plasma concentrations of imipramine (IP) and its active metabolite desipramine (DMI) applicable to larger clinical studies there has been an increasing interest in studying the use of plasma concentrations in controlling the therapy. Better knowledge of the pharmacokinetics would perhaps explain, at least in part, the large number of nonresponders (30–40%) found in most clinical trials with IP as well as other tricyclic antidepressants (Benett, 1967). A recent review concluded that the studies on the relationship between plasma level and clinical effect for various types of tricyclic antidepressants published so far are not conclusive, and that the whole area presents great methodological problems that need to be carefully considered (Gram, 1977).

In a previous report (Gram et al., 1976) on 24 patients receiving imipramine treatment we found critical lower limits for the plasma concentration of each of the two active compounds (IP and DMI). All nonresponding or partially responding patients had plasma concentrations of IP or DMI, or both, below these limits, whereas the responding patients had plasma levels of both compounds above these limits.

The present report collects the results for the first 24 patients and the following 42 patients – 66 patients

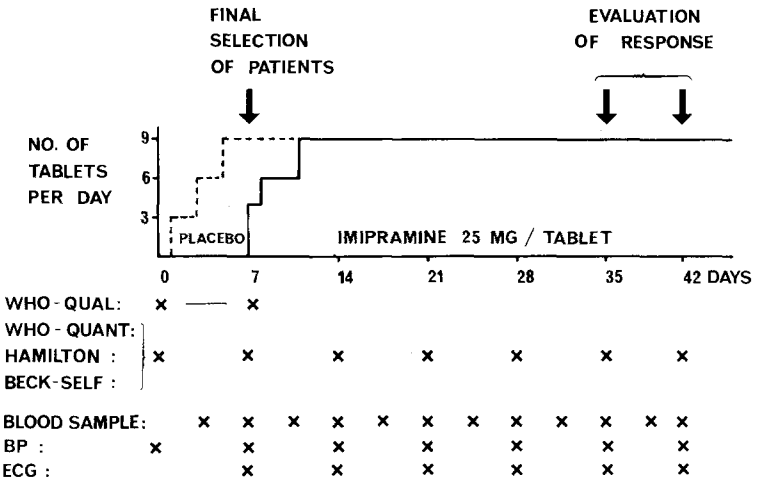

Fig. 1. General design of imipramine plasma level/effect study

in all. As there were only minor differences in terms of age and sex distribution, response rate, and diagnostic classification between the two parts of the study, it was considered justifiable to pool the data.

Besides pointing out a strong relationship between kinetics and clinical effects, the study identifies several pharmacokinetic as well as clinical methodological problems involved in such studies.

MATERIALS AND METHODS

General Design. The study was carried out as a multicenter study during a period of 27 months at one Swedish and three Danish psychiatric units. A total of 121 patients aged 18–65 years with depressive illness needing hospitalization were screened for the study before antidepressive treatment began. Of the 102 patients who fulfilled the selection criteria, 66 of these, 46 women and 20 men, completed the study. Fifteen patients came from Department II, Lillhagen Hospital, Gothenburg (Nos. 101–123), 39 from the Municipal Hospital, Copenhagen (Nos. 301–361), five from Rigshospitalet, Copenhagen (Nos. 501–507), and seven from Department P, State Mental Hospital, Glostrup (Nos. 601–610).

The general design of the study is shown in Figure 1. After a placebo period of 7 days, IP was administered in increasing doses over 4 days to reach a standard dose of 225 mg/day. This dose was maintained to Day 35; i.e., maximum dose was given for three and a half weeks. The period of observation could be prolonged by 1 or 2 weeks or more.

Before active treatment (between Day 0 and Day 7) the patients were scored on the WHO Diagnostic Depression Scale (Sartorius, 1974). Before, and once weekly during the treatment, Hamilton's Rating Scale (HRS) (Hamilton, 1960), the WHO (Quantitative Part), and a side-effect scale were used, and the patients completed the Beck Depression Inventory (Beck et al., 1961). The ratings were carried out each test day in the morning between 8 a.m. and 10 a.m. At Day 35 the patients were classified as responders, partial responders, or nonresponders according to the scores on the rating scales.

To ensure homogeneity in the use of the rating scales, joint rating sessions were performed prior to the study. Fifteen patients were rated by four psychiatrists to a standard deviation (s) on total score = 2.8. Further, two joint ratings were performed during the study. Psychiatrists joining the study group were trained before performing rating.

Blood samples for measurement of IP and DMI were drawn twice weekly.

Inclusion Criteria. The inclusion criteria were quantified as follows, according to the HRS score on Day 7, i.e., at the end of the placebo period:

1) Item No. 1 (depressed mood) $\geqq 1$

2) Item Nos. $1 + 2$ *or* Item Nos. $1 + 8$ *or* Item Nos. $2 + 8 \geqq 4$ (No. 1: depressed mood, No. 2: guilt, No. 8: retardation)

3) Total HRS (Item Nos. 1–17) $\geqq 19$, *or* Total HRS $\geqq 16$, and Subscale Score $\geqq 9$.

The subscale consists of Items Nos. 1, 2, 7, 8, 10, and 13 (depressed mood, guilt, work and interest, retardation, psychic anxiety, and general somatic complaints). These items have been shown to be those correlating best with a global assessment of depression (Bech et al., 1975).

Exclusion Criteria. Patients with severe anxiety and clouded consciousness or severe motor retardation (stupor) were excluded. According to the routine of the participating departments, these patients were treated with ECT. Patients with histories of drug abuse, patients with delusions or hallucinations of nondepressive nature, and patients with depression of more than 12 months' standing were all excluded from the study. According to generally accepted practice, patients with affected liver functions or cardiac diseases were also excluded.

Excluded Patients. Thirty-six patients were excluded during the placebo period or later for reasons indicated in Table 1. In most cases exclusion was chosen because the patients did not fulfill the criteria for inclusion on Day 7. In four cases the IP-treatment had to be discontinued and the patient had to be transferred to ECT treatment.

Diagnostic Classification. The diagnostic classification of the patients was worked out on the basis of the WHO scale (Sartorius, 1974). As a scoring system for this scale is still under preparation, the item scores from the WHO scale were transferred to the relevant items in the Newcastle Diagnostic Scale (Newcastle I, Carney et al., 1965; Carney and Sheffield, 1972; Newcastle II, Gurney et al., 1972; Kerr et al., 1972). A detailed description of this transformation will be published elsewhere (Bech et al., unpublished). The patients were scored on the Newcastle I scale as neurotic: 0, intermediate:

Table 1. Patients excluded after Day 0

Reasons for exclusion	N
Did not fulfill the criteria of inclusion – excluded day 7 (301, 307, 314, 317, 321, 323, 324, 326, 329, 332, 340, 341, 342, 358, 359, 503, 601, 605)	18
Transferred to ECT treatment (119, 122, 306, 343)	4
Suicide – day 10 (330)	1
Disclosure of criteria of exclusion	
Cardial disorder (320, 325, 356)	3
Symptoms of drug abuse (111, 112, 336)	3
Schizophrenic symptoms (506)	1
Other (110, 116)	2
Side effects	
Change to mania (109)	1
Increasing hepatic enzymes (602)	1
Deviation from the protocol	
Additional drug intake (113)	1
Omission of drug intake (102)	1
Total	36

1, depressive: 2, and on the Newcastle II as reactive: 0, intermediate: 1, depressive: 2. From the sum of these scores the patients were characterized as 'non-endogenous' depressions: 0–2, and 'endogenous' depressions: 3–4.

The classification of the patients as unipolar or bipolar depressions had to be abandoned because only 17 patients could be unanimously placed according to the criteria of Perris (1968).

Evaluation of Therapeutic Effect. Clinical response was defined in the protocol as a posttreatment HRS score ≤ 7. Patients with HRS: 8–15 were classified as partial responders and patients with a posttreatment HRS score ≥ 16 as nonresponders.

In studies comparing scores of rating scales for global clinical assessment it has been found that clinical recovery (no depression) corresponds to HRS Total Score ≤ 7, HRS Subscale Score ≤ 4, Beck's Self-Rating Score ≤ 8, and WHO Quantitative Part ≤ 16 (Bech et al., 1975; Bech et al., unpublished).

Analogous to this, the partially responding patients could be characterized by HRS Total: 8–15, HRS Subscale: 5–9, Beck's Self-Rating: 9–20, and WHO Quantitative Part: 17–30.

The patients were followed to Day 35 – except for three patients who recovered at an earlier date and were discharged (Nos. 310, 315, and 604) and four nonresponding patients who were transferred to other treatment after Day 28 (Nos. 106, 113, 322, and 354). In these cases the observation was ended on Day 28. In 13 cases the patients were followed without additional treatment on unchanged or reduced dose of IP until Day 42 (Table 3).

Rating of Side Effects. Before treatment and once weekly the following symptoms were rated on a 0-1-2 scale: tiredness-fatigue, headache, orthostatic dizziness, vertigo, tremor, palpitations, perspiration, blurred vision-disturbed accomodation, dry mouth, thirst, nausea-vomiting, miction disturbances, constipation, and sexual dysfunction. Blood pressure (BP) in lying and upright posture, and electrocardiogram (ECG) was recorded once weekly. Complete BP data was obtained in 59 patients.

Aspartate-aminotransferase (liver enzyme) was assayed three times throughout the treatment period.

Medication and Plasma Level Measurements. The tablets (placebo and imipramine hydrochloride 25 mg – Tofranil®) were given at 8 a.m., 1 p.m., and 5 p.m. The patients were observed ingesting the tablets. Patients, nursing staff, and psychiatrists not involved in the study did not know that placebo tablets were given during the first week (Fig. 1). Nitrazepam 5–15 mg was allowed as a hypnotic and/or sedative. Available data indicate that benzodiazepines given in these doses do not significantly influence the metabolism of tricyclic antidepressants (Silverman and Braithwaite, 1973; Gram et al., 1974). Approximately 60% of the patients were given this drug, in almost all cases in a dose of 5–10 mg before sleep. No other medication was allowed.

In one case (No. 308) the IP dosage was fixed at 150 mg/day due to low body weight. In 14 cases the dose was reduced before Day 35 (Table 3). In 4 cases (Nos. 104, 310, 502, and 604) this was done because the patient had responded, in 4 cases because the patients were transferred to other treatment (ECT or supplementary medication), and in 6 cases because of side effects.

Blood samples were taken from fasting patients at 8 a.m., 15 h after last intake of IP. IP and DMI in plasma were assayed by quantitative in situ thin-layer chromatography with some modification of the method described by Nagy and Treiber (1973).

For correlation with clinical effects at Day 35 the mean value of the plasma concentrations at Days 21, 28, and 35 was calculated. For patients followed to Day 28 only the mean value of Days 21 and 28 was used.

Analysis of Data. According to the protocol, posttreatment HRS scores were correlated to the plasma concentration measurement of IP and DMI by

a) calculating the sum of IP + DMI, or
b) by weighting the potency of each drug by multiplication (of each concentration value) with factors between 0.1 and 10 before calculating the sum, or
c) by drawing isobolographic plots according to Gessner (1974).

Similar analyses were also completed for the side-effect score, the blood-pressure values, and weight changes. In these cases the differences between values obtained during treatment and during placebo (Day 7) were calculated.

The relationship plasma level/rating scores was tested by nonparametric correlation analysis (Spearman rank correlation), whereas statistical calculations on the results relating to the proposed plasma level limits were considered not fully meaningful or justified because these limits were determined a posteriori. Changes in rating scores were statistically tested by use of Wilcoxon test for pair differences.

RESULTS

Clinical Effects. Twenty-one patients showed full response (HRS ≤ 7) at Day 35 or earlier. Twenty-three were partial responders (HRS: 8–15) at Day 35, and six of these recovered in the fifth week before Day 42. Twenty-two patients were scored as nonresponders (Table 2). Thirty-seven patients were classified as 'endogenous' depressions according to the criteria based on the Newcastle scales, and twenty-nine patients as 'non-endogenous' depressions. There were no statistically significant differences in the response rate between the two diagnostic groups.

In Table 2 the two diagnostic groups have been described according to sex, age, and response. It can

Table 2. Distribution according to diagnostic classification, sex, and response in 66 patients treated with imipramine. Age indicated as mean of each group (see also Table 3)

Diagnostic classification	Sex	Responders (HRS ≦ 7)		Partial responders (HRS: 8–15)		Nonresponders (HRS ≧ 16)		Total	
		N	age	*N*	age	*N*	age	*N*	age
'Endogenous'	f	11	56	5	53	8	47	24	52
	m	1	32	6	50	6	50	13	48
	f + m	12	54	11	51	14	51	37	51
'Non-endogenous'	f	5	41	10	47	7	38	22	43
	m	4	35	2	59	1	57	7	45
	f + m	9	38	12	49	8	40	29	43

f: female, m: male

Table 3a. Plasma concentrations and clinical effect for 'Endogenous' depressions, grouped according to response

	No.	Sex	Age	HRS			Beck total	WHO total	Plasma conc.		Note
				total	subsc.	%			IP	DMI	
Responders	104	f	58	0	0	0	0	0	268	139	b
	108	m	32	7	4	32	13	7	61	256	b
	117	f	53	6	1	38	5	6	116	161	
	310	f	64	7	3	32	6	7	69	127	a, c
	312	f	56	6	4	6	4	13	223	126	
	315	f	49	5	1	24	8	9	56	214	c, k
	347	f	57	6	3	40	4	10	73	171	
	355	f	54	7	4	29	7	11	109	155	
	502	f	64	1	1	5	4	2	56	675	a, b
	606	f	52	1	0	3	0	1	50	258	
	607	f	56	4	0	10	7	6	48	408	
	609	f	58	2	1	8	6	1	64	88	
Partial responders	115	m	58	11	5	69	11	12	39	33	
	118	f	53	11	1	42	9	15	51	100	g, h
	302	f	57	12	5	56	13	21	83	115	g, h
	311	f	34	15	5	94	30	30	32	119	
	318	m	25	11	6	61	13	18	16	39	
	319	f	55	12	6	67	4	19	61	313	g
	339	m	54	12	6	44	14	28	117	492	
	349	m	39	13	4	68	17	24	6	55	
	351	m	49	11	6	40	5	26	33	80	
	353	m	62	11	5	52	10	21	47	496	a, g, h
	610	f	65	11	6	32	21	12	127	495	g, h
Nonresponders	106	m	46	20	12	80	22	30	106	20	d
	107	m	35	e	e	e	e	e	36	82	a, b, e
	304	m	53	24	13	89	39	42	58	39	
	316	f	53	24	13	92	—	41	107	66	
	322	f	55	34	15	162	31	49	69	106	d
	344	f	53	18	13	86	11	38	65	163	g, j
	346	f	28	21	10	88	23	38	26	52	
	352	f	29	19	9	100	23	33	27	112	
	354	m	61	23	11	93	34	40	90	60	d
	357	m	57	19	10	86	35	35	38	191	
	360	m	51	33	17	117	32	50	41	131	
	361	f	37	19	9	86	14	31	92	66	
	501	f	54	24	14	73	23	42	54	166	a, g, j
	507	f	65	19	11	76	43	32	30	90	a, h

Table 3b. Plasma concentrations and clinical effect for 'Non-endogenous' depressions, grouped according to response

	No.	Sex	Age	HRS			Beck total	WHO total	Plasma conc.		Note
				total	subsc.	%			IP	DMI	
Responders	101	m	64	3	2	17	5	1	68	135	
	114	f	23	7	3	41	14	14	87	357	
	123	f	43	5	3	27	6	10	110	94	
	303	m	21	5	2	24	23	14	166	282	
	305	m	36	1	1	6	10	3	47	108	
	348	f	59	5	2	24	16	10	33	112	
	505	m	19	4	3	36	2	6	30	57	
	604	f	33	7	5	26	11	7	25	138	b, c
	608	f	44	4	2	21	0	3	40	83	
Partial responders	105	f	35	9	4	75	8	12	24	81	
	121	f	51	14	7	64	22	18	55	196	g
	308	f	62	11	3	52	8	20	35	58	a
	309	f	64	11	5	50	4	16	57	184	b, g, h
	313	f	48	8	6	42	13	13	35	461	
	331	f	20	10	4	48	18	20	90	156	g
	333	f	33	14	9	70	28	39	34	104	
	334	m	54	11	5	44	12	21	116	361	g, h
	335	f	50	10	4	48	20	18	117	18	
	337	f	57	13	5	59	7	14	50	118	g
	504	m	63	12	7	71	2	15	137	57	
	603	f	54	13	9	59	19	17	148	133	g
Nonresponders	103	f	30	17	7	71	11	24	33	201	
	113	f	27	23	13	70	31	27	195	54	d
	120	f	25	17	5	89	21	29	50	36	
	327	f	39	17	9	94	8	30	35	33	
	328	f	54	29	16	121	–	52	53	117	
	338	m	57	18	8	90	18	39	48	125	
	345	f	33	23	9	85	24	46	32	50	
	350	f	56	16	9	64	27	32	21	63	

The first figure in patient number refers to participating department (see text). f = female, m = male
Scores on Hamilton Rating Scale (HRS) are given for Day 35 except for 7 patients (see text) where Day 28 results are given. Total = total score (17 items), Subsc. = subscale score consists of results of items Nos. 1, 2, 7, 8, 10, and 13, % = Day 35 total score in percent of total score on Day 7
Total score on Beck's Depression Inventory consists of the sum of 21 items, and a total score of WHO depression scale (quantitative part) consists of the sum of 38 items
Plasma concentrations for imipramine (IP) and desipramine (DMI) are given in µg/l as the mean of results for Days 21, 28, and 35 (see text)

Abbreviations in note:
[a] Dose reduced before Day 28
[b] Dose reduced Day 28–35
[c] Discharged after recovery, last rating Day 28
[d] Transferred to other treatment, last rating Day 28
[e] Dissimulating, HRS score Day 28: 19, score Day 35: 6, suicide 3 days later
[g] Followed to Day 42 on unchanged or reduced dose of IP
[h] Patient recovered Day 42 on unchanged or reduced dose of IP
[j] Partial response Day 42 on unchanged or reduced dose of IP
[k] Hypomanic, rating scores given from Day 28

be seen that the patients with typical 'endogenous' depressions were in average 8 years older than the patients classified as 'non-endogenous' depressions ($P < 0.05$, Mann Whitney U-test). There were in general no differences between the two sexes regarding the type of response.

The classification of patients into responders, partial responders, and nonresponders was generally not much influenced by the choice of scale (Table 3).

Analyses of the scores on the side-effect scale revealed that, in particular, scores on items representing assumed anticholinergic effects (blurred vision,

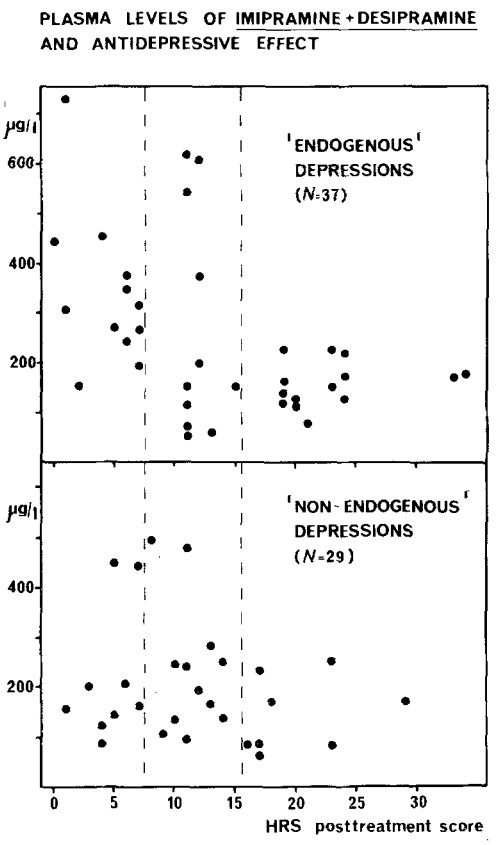

Fig. 2. Hamilton Rating Scores (HRS) and plasma concentration of imipramine + desipramine after 4 weeks (Day 35) of active treatment. For 7 patients the concentration at Day 28 is used (see text)

dry mouth, miction disturbances, constipation) changed consistently during active therapy. The total score on these four items increased significantly ($P < 0.01$) from Day 7 to Days 14–21 (mean). Increased score was particularly pronounced in partial and nonresponding patients of 'endogenous' type. Fifty-five percent of the patients with an initial rise in score showed a subsequent decrease in score on Days 28–35. For the whole group of patients the total scores (4 items) on Days 28–35 (mean) were still significantly higher than at Day 7 ($P < 0.05$).

Weight changes ranged from -4.5 to $+7.5$ kg with a majority of patients having some weight gain.

The occurrence of orthostatic BP effects increased from about 30% at Days 14–21 to about 50% at Day 35. In four cases such symptoms caused a reduction of IP-dose.

No marked changes in ECG were observed. One patient was excluded due to rise in liver enzymes in plasma.

Plasma Level/Clinical Effect Relationship. Steady-state plasma concentrations were obtained within 7 to 21 days of treatment with IP, and subsequently the plasma concentration stayed relatively stable (Gram et al., 1977) unless the dose was changed.

The IP concentration ranged from 6 to more than 300 μg/l, and the DMI concentration from 15 to about 700 μg/l.

The mean levels from Day 21 to Day 35 (in six patients Day 21 to Day 28) are given in Table 3.

The conventional way of relating plasma levels of drugs and their active metabolites to the clinical effect is to relate each compound or their sum to the effect. Such an analysis of the present data is shown in Figure 2. There was a significant negative correlation between HRS posttreatment scores and IP + DMI plasma levels in the group of 'endogenous' depressions ($r_s = -0.51$, $P < 0.01$), but no correlation in the group of 'non-endogenous' depressions ($r_s = -0.13$, NS). All nonresponders, irrespective of diagnostic classification, had plasma levels of IP + DMI below 240 μg/l. Regarding the responders and partial responders there was some overlap, but most of the responders in the 'endogenous' group had plasma levels above this limit.

As shown by Gessner (1974), data relating to two active compounds should preferably be analysed on an isobologram as shown in Figures 3 and 4. It was indicated in our first report (Gram et al., 1976) that a better relationship between effect and plasma level is obtained when it is assumed that both active compounds have critical lower plasma level limits.

Both of these two methods of data analysis gave a good differentiation between responders and nonresponders. In Table 4 two plasma-level limits for differentiation have been indicated. The lower limit defines the lowest level in responding 'endogenous' depressed patients. The upper limit defines the highest level in nonresponding 'endogenous' depressed patients. For the sum (IP + DMI) these limits were 150 and 240 μg/l respectively. Analysed separately (isobologram), the limits for IP of 45 and 70 μg/l respectively, in connection with a DMI limit of 75 μg/l, represent the corresponding lower and higher plasma level limits as defined above.

A third way of analysing the data is to assume that the two active compounds are qualitatively equal, but have a different potency in relation to the plasma concentration measurement. If this is the case, straight lines on the isobologram should differentiate between responders and nonresponders, and the slope of this line would indicate the relative potency of the two compounds. Analysed in this way, the data indicate that IP is two to four times as potent as DMI in relation to their plasma levels. However, the results of weighting the plasma concentration measurement according to this method did not differ much from

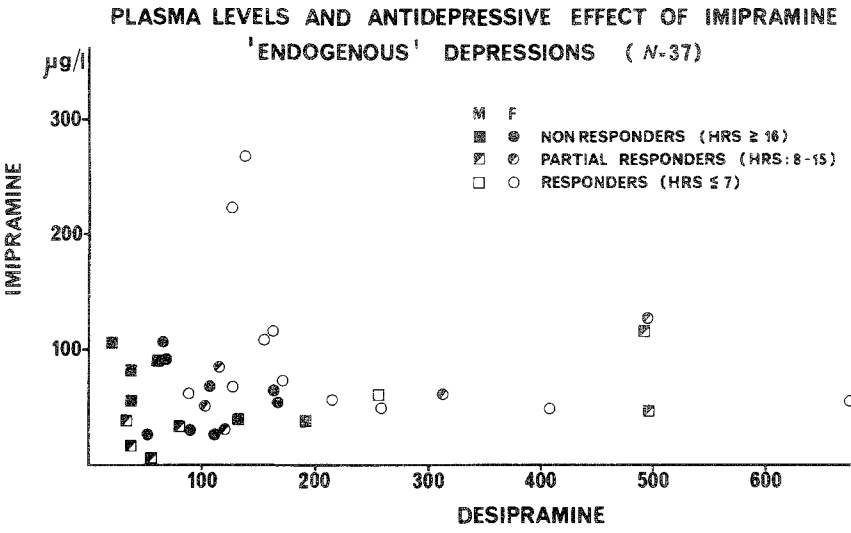

Fig. 3. 'Endogenous' depressions. Relationship between posttreatment (Day 35) score on Hamilton's Rating Scale (HRS) and plasma levels of imipramine and desipramine

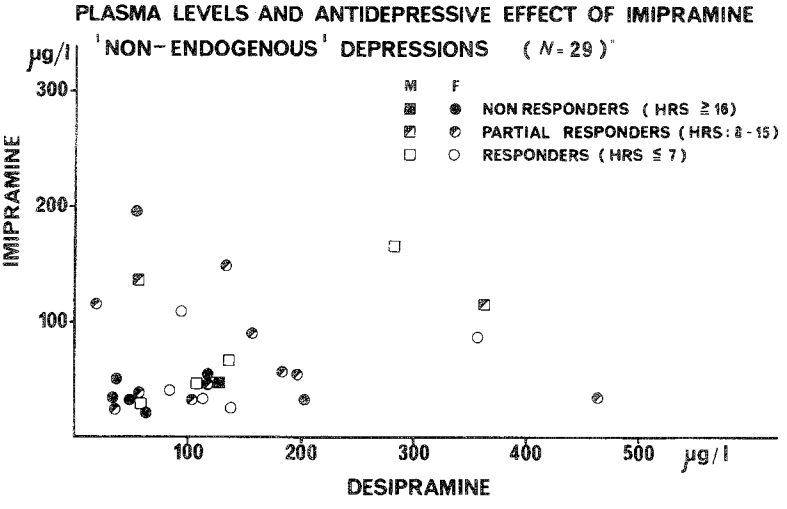

Fig. 4. 'Non-endogenous' depressions. Relationship between posttreatment (Day 35) score on Hamilton's Rating Scale (HRS) and plasma levels of imipramine and desipramine

Table 4. Plasma level limits differentiating between responders, partial responders, and nonresponders in 'endogenous' and 'non-endogenous' depressions respectively

Plasma level limits (µg/l)	'Endogenous' depressions			'Non-endogenous' depressions			Totals		
	R	PR	NR	R	PR	NR	R	PR	NR
IP > 45 *and* DMI > 75	12	6	3	5	6	2	17	12	5
IP < 45 *and/or* DMI < 75	0	5	11	4	6	6	4	11	17
IP + DMI > 150	12	7	7	6	10	4	18	17	11
IP + DMI < 150	0	4	7	3	2	4	3	6	11
IP > 70 *and* DMI > 75	5	4	0	3	3	0	8	7	0
IP < 70 *and/or* DMI < 75	7	7	14	6	9	8	13	16	22
IP + DMI > 240	10	4	0	3	6	1	13	10	1
IP + DMI < 240	2	7	14	6	6	7	8	13	21
Totals	12	11	14	9	12	8	21	23	22

R = Responders (HRS ≦ 7); PR = Partial responders (HRS: 8–15); NR = Nonresponders (HRS ≧ 16)

the other methods of relating plasma levels and therapeutic effect.

Using plasma levels from Day 35, or from the time of recovery, gave essentially the same conclusions regarding plasma level/effect relationship as those described above.

As discussed elsewhere (Gram et al., 1977), patients at ages below 50 had significantly lower plasma levels of IP and IP + DMI compared to patients above 50 years of age. The relationship between effect and plasma levels was, however, completely clear when the two age groups were analysed separately, thus emphasizing that the plasma level is the critical variable most directly related to the clinical outcome (Table 3).

Table 4 and Figures 2, 3, and 4 show that the plasma level/effect relationship in the group of patients classified as 'non-endogenous' was much less clear than that in the 'endogenous' group. The 'non-endogenous' group was particularly characterized by a larger number of responders with plasma levels below the lower critical limit discussed above.

The predictive value of the plasma levels at Day 14 after 1 week of IP treatment was examined. Using the lower critical limit of the sum of IP + DMI (< 150 µg/l), it was possible to predict the response in the 'endogenous' depressed group. Eleven out of 12 responders were above this limit, and 16 out of 25 partial or nonresponders were below it. Correspondingly, 10 out of 12 responders were above the limits of IP $\leqslant$ 45 µg/l and DMI $\leqslant$ 75 µg/l, and 15 out of 25 partial or nonresponders were below it.

Drug-related effects on BP were in particular detectable in relation to an increase in the orthostatic changes (diminution of systolic pressure and amplitude). There was some correlation between plasma level and increase of these orthostatic effects that was seen more frequently in the patients with the highest plasma levels.

There was no clear relationship between plasma levels and increase from Day 7 to Days 14–21 in score on items covering anticholinergic symptoms. Isobolographic plots showed that neither high IP nor high DMI concentrations were associated with particularly high incidence of anticholinergic effects. The weight change did not correlate clearly with the plasma levels.

DISCUSSION

The overall clinical effect of IP in this study was fully comparable to that reported from many other clinical trials with IP (Benett, 1967). About 30% of these hospitalized depressed patients were full responders and a total of 70% showed full or partial response at Day 35.

The plasma level/effect relationship indicated in this report is generally the same as that indicated in our preliminary report on the first 24 patients (Gram et al., 1976). In accordance with Glassman et al. (1975b) our results strongly indicate that high plasma levels of IP and/or DMI are *not* associated with unfavourable therapeutic effects as indicated in studies with nortriptyline (Åsberg et al., 1971; Kragh-Sørensen et al., 1973, 1976; Ziegler et al., 1976a) and with protriptyline (Whyte et al., 1976).

If the following critical lower limits are chosen: IP < 45 µg/l and/or DMI < 75 µg/l, four full responders (Nos. 348, 505, 604, and 608) are found below these limits. All of these were 'non-endogenous' depressions (Table 4). Some of them may represent spontaneous remissions [e.g., No. 505 (Gram et al., 1976)] or would have been reported as only partial responders if other scales had been used for response classification (Table 3).

On the other hand, 17 partial nonresponders had plasma levels above these limits (Table 3). Some of these might have responded if the treatment had been prolonged at Day 35. In fact, 11 of these patients were followed with ratings to Day 42 on unchanged or reduced IP dose. Of these, 6 (118, 302, 309, 334, 353, and 610) were full responders, and 2 (344 and 501) changed from none to partial response at Day 42.

Different ways of analysing the plasma level measurements of IP and DMI in relation to the therapeutic effect gave only modest differences (Table 4). The way IP and DMI interact is not clear from this study.

This study points to a clear clinical significance of measuring plasma levels of IP and DMI as a tool in therapy control, but more studies are needed in this field. In particular, studies on the effect of dose and plasma level adjustments are needed. However, a number of methodological factors that seem to be important in studies of this kind deserve more attention and elucidation.

Because it was considered desirable to study a patient population with as great a range in plasma levels as possible, this study was designed with a fixed-dose schedule and not with a dosage per weight as done by other groups (Glassman et al., 1975b). Such a procedure would decrease the range of the plasma level. Also, a dose regimen based on the occurrence of side effects (Ziegler et al., 1976a, b) seems unfavourable, because it would decrease the mean and range of plasma levels. On the other hand, the use of a fixed dose schedule may cause problems with side effects and the need for dose reduction. In patients having their dose reduced it might be difficult to determine the level at which the drug executed its effect. Considering that the antidepressive level is not instanta-

neous, we preferred to use a mean level covering the last 2 weeks of treatment. Ideally, then, patients having their dose changed should have been followed on the new steady-state level for an appropriate time, but this procedure would introduce a time factor and was generally not feasible.

It should be noted that the term 'non-endogenous' was chosen for this group of reactive, neurotic, doubtful, or atypical depressions in order to differentiate from the core group of typical or classical 'endogenous' depressions.

Obviously, the therapeutic effect was a graduated effect and not an all-or-none reaction. Thus, the classification of patients as responders, partial responders, and nonresponders is arbitrary. As shown in Table 3, no particular scale or mode of calculation had any advantage in this respect.

It has been discussed whether the posttreatment score is the most relevant measure of the antidepressive effect (Hamilton, 1966). In this study an improvement to 40% or less of the pretreatment score (Table 3) gives a higher statistical variation and essentially no change in the judgement of the response.

It is interesting to note that discrepancies between scales were seen more frequently in 'non-endogenous' depressions than in 'endogenous' depressions (Table 3). The patients classified as 'non-endogenous' depressions were much more hesitatant in scoring themselves as cured than were the clinicians.

The partial responders present some interesting problems. They might represent a group of slowly responding patients. It has been mentioned that at least 6 (out of 13) patients recovered on Day 42 on an unchanged or slightly reduced dose.

As some had a high plasma concentration, it was examined whether side effects could have obscured the therapeutic effect. This appeared not to be the case.

It has been claimed that delusional depressive patients do not respond to IP (Glassman et al., 1975a). We found, however, that 17 patients showing one ($N = 11$) or more ($N = 6$) delucional symptoms on the WHO scale at Day 7 were equally distributed on the three groups with full, partial, or nonresponse.

As mentioned above, the duration of the treatment period is of importance in studies of plasma level/effect relationship. Many patients responded during the fifth week if the treatment was prolonged unchanged. This would indicate that generally it appears desirable to extend the period of study to at least 5 weeks. On the other hand, a longer duration of trials increases the chance of spontaneous remissions and the probability of finding responders with plasma levels below the critical limits.

The methodological factors concerning kinetics, clinical methodology, and design discussed above and elsewhere (Glassman et al., 1973; Gram, 1975, 1977) need to be considered in future studies in this field. It seems possible, then, to reach conclusions of immediate clinical importance.

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