CONTROLLED STUDY COMPARING NOMIFENSINE AND CLOMIPRAMINE IN UNIPOLAR DEPRESSION, USING THE PROBENECID TECHNIQUE

J.D. VAN SCHEYEN

Department of Psychiatry, Hospital 'Gasthuis', Middleburg, The Netherlands

H.M. VAN PRAAG & J. KORF

Department of Biological Psychiatry, Psychiatric Clinic, State University, Groningen, The Netherlands

- 1 Central dopamine turnover may be lowered in patients with unipolar endogenous depression, particularly when associated with retardation.
- 2 Nomifensine selectively activates the central dopaminergic system and may be of special therapeutic value in patients with motor inhibition.
- 3 A double-blind comparison of clomipramine and nomifensine was carried out in patients with recurrent unipolar depression. Biochemical and clinical assessments were carried out weekly for 4 weeks.
- 4 The mean homovanillic acid level in cisternal liquor of those patients who responded to nomifensine, was significantly lower than the mean level of the total group.
- 5 The factor 'retardation' on the Hamilton Depression Scale was improved more with nomifensine than with clomipramine.

Introduction

According to the so-called 'monoamine hypothesis', central monoaminergic hypoactivity occurs in unipolar, vital (endogenous) depression. This specifically implies hypoactivity of the central serotonergic and/or dopaminergic and noradrenergic systems. Investigation of the cerebrospinal fluid (CSF) metabolites of the relevant neurotransmitters, namely 5-hydroxytryptamine (5-HT), dopamine (DA) and noradrenaline (NA), seems on the basis of previous investigations to support the hypothesis (van Praag, 1974).

Studies by van Praag and others have shown that the turnover of DA in depressive patients may be lowered—in particular, when motor inhibition (for example, psychomotor inhibition, retardation and apathy) are prominent (Korf & van Praag, 1971a; van Praag *et al.*, 1973).

L-DOPA, a substance which, in the brain, is converted mainly into DA, has a therapeutic effect in these patients—in particular, where motor pathology is concerned (Goodwin *et al.*, 1970).

The investigation of cerebral monoamine metabolism is facilitated by the probenecid technique. Probenecid inhibits the transport of the acid monoamine metabolites from the CNS to the blood stream.

This results in an accumulation of 5-

hydroxyindoleacetic acid (5-HIAA) and homovanillic acid (HVA), which are the metabolites of 5-HT and DA, respectively. The speed of accumulation is a measure of the turnover of the corresponding monoamines. A low rate of accumulation indicates a low rate of production of the metabolites. This reflects a diminished breakdown, and therefore a low turnover, of the monoamines. A high rate of accumulation indicates the reverse—that is, a greater breakdown and a larger turnover of the monoamines. The concentration of the metabolites 5-HIAA and HVA is not only dependent on the speed of their production but also on the quantity of probenecid entering the CNS.

The more probenecid in the CSF, the greater the accumulation of 5-HIAA and HVA. Investigations by van Praag (1974) have shown that the maximal, that is, optimal, quantity of probenecid is reached after oral administration of 5 g over 5 hours. The standard probenecid technique involves the measurement of the relevant metabolites in the lumbar CSF before administration of probenecid and 4 h after the last dose of probenecid.

Van Praag *et al.* (1973) have shown that the accumulation of 5-HIAA and HVA in 38 depressive patients was significantly smaller when compared with 12 normal subjects. Comparable results were

described by Goodwin *et al.* (1973) and by Persson & Roos (1969).

In these studies the concentration of metabolites in the lumbar CSF was investigated. A false picture of cerebral monoamine metabolism, however, may have emerged because it is known that 5-HIAA, for example, is also produced in the spinal cord (Bulat *et al.*, 1971).

As a result, we decided that the investigation of cisternal CSF is a more rational means of estimating cerebral monoamine metabolism. Nomifensine selectively stimulates postsynaptic DA receptors (Costall *et al.*, 1975). Furthermore, there are indications that nomifensine significantly blocks the central re-uptake of DA out of the synaptic cleft.

Because of these biochemical properties it is to be expected that the substance will have an antidepressant activity—in particular, in patients with motor inhibition. Such patients may be expected to have lowered DA turnover in the brain.

Methods

The hypothesis mentioned above was tested in this investigation. The control group consisted of a group

of depressive patients who were treated with the antidepressant, clomipramine. In all patients, DA and 5-HT turnover was investigated before starting medication, using the probenecid technique. A total of 5 g probenecid was administered (1 g every hour starting at 0800). Four hours after the last dose of probenecid, a cisternal puncture was carried out. In the CSF thus obtained, the concentration of HVA, 5-HIAA and probenecid was measured, as described by Westerink & Korf (1975). Korf and van Praag (1971b), and Korf *et al.* (1973).

The investigation was carried out in a double-blind manner using a non-crossover design with a fixed dosage scheme. Patients were allocated to either nomifensine or clomipramine at random on admission to hospital. Medication was given in gradually increasing doses over 5 d, up to 50 mg orally three times daily, and was continued for 4 weeks. Active drugs were presented in identical capsules.

Twenty-two patients (age range 21–65 yr) have already been investigated, 12 patients receiving nomifensine and 10 clomipramine. These were all patients with unipolar, vital depression of such severity that clinical treatment was indicated. All the patients showed inappropriate depression of mood and at least three of the following symptoms: (1)

Table 1 Baseline patient data on admission to study

Patient	Age	Sex	Previous depressions	Medication	HVA (ng/ml)	5-HIAA (ng/ml)	Probenecid (µg/ml)
1	56	M	3	N	149	74	11.5
2	21	M	—	N	42	62	8.0
3	38	F	—	N	174	98	21.0
4	53	F	—	N	269	127	18.8
5	44	M	—	C	237	121	16.7
6	64	F	2	N	300	158	25.9
7	42	F	—	N	342	163	24.2
8	59	F	1	C	195	69	12.0
9	57	M	—	N	192	110	18.3
10	33	M	1	N	165	93	14.7
11	54	F	3	C	234	116	17.3
12	27	F	1	C	296	93	14.5
13	47	F	4	C	308	59	19.3
14	63	M	1	C	333	93	14.6
15	53	M	3	N	—*	—*	—*
16	51	F	1	C	468	123	18.5
17	61	F	2	C	263	99	15.2
18	34	M	3	C	355	95	18.3
19	39	F	1	N	247	80	11.7
20	35	F	1	C	244	103	17.6
21	51	M	2	N	265	145	10.0
22	57	F	2	N	354	197	21.7
Totals					258.7† (42–468)	108.5† (59–197)	16.7† (10.1–25.9)

N, Nomifensine; C, clomipramine.

* No CSF obtained; † mean + range.

Figure 1 Cisternal CSF HVA levels (ng/ml) on admission to study, distributed according to treatment group and response to treatment. a, Nomifensine; b, clomipramine.

diurnal variation of mood; (2) pathological guilt; (3) lack of energy; (4) loss of appetite; (5) early morning waking.

A history of previous episodes of depression was known for 16 out of the 22 patients (Table 1). Patients with obvious organic disability were excluded from the study. The therapeutic effect was studied over a period of 4 weeks' medication.

Besides routine clinical evaluation, patients were assessed using the Zung and Hamilton Depression Scales on days 0, 7, 14, 21 and 28 of the trial. In addition, all these patients had weekly haematological and biochemical screening: white cell count, ESR, SGOT, SGPT, and alkaline phosphatase and γ -GT (γ -glutamyl transpeptidase) tests.

Results

Results are shown in Table 1 and Figures 1 and 2. It was striking that CSF pressure was reduced in all patients at the time of suboccipital puncture, with the result that this had to be carried out in the majority of cases with the patient in a slight Trendelenburg position. No CSF was obtained in one patient (number 15). After puncture, the CSF was immediately frozen at -25°C .

The number of patients showing a positive reaction after 4 weeks' medication was relatively low in both groups, five from the nomifensine group and three

Figure 2 Cisternal CSF 5-HIAA levels (ng/ml) on admission to study distributed according to treatment group and response to treatment. a, Nomifensine; b, clomipramine.

from the clomipramine group (Figures 3 and 4; Table 2). Patients reacting positively to nomifensine improved further after continued administration of nomifensine in the out-patients department. The same was also true for the clomipramine patients.

Figure 3 Mean total Hamilton Depression Scale scores before and at weekly intervals during treatment with nomifensine. Δ , All patients; $\bullet$, responders ($n = 5$).

Figure 4 Mean total Hamilton Depression Scale scores before and during treatment with clomipramine. Δ, All patients; ▲, responders ($n=3$).

Figure 5 Mean scores for factors 7 and 8 in the Hamilton Depression Scale analyzed according to treatment group. Δ, Nomifensine; ▲, clomipramine

In two patients in the nomifensine group (numbers 6 and 21), depression deteriorated into a state of severe, agitated melancholia within 2 weeks after admission, with the result that electroconvulsive therapy (ECT) had to be given. A number of poor responders eventually showed improvement after a period of 4 weeks, either with other antidepressant or with ECT and/or sleep deprivation.

We investigated whether there was any correlation between the factors inhibition—for example, retardation, HVA level in the CSF, and the therapeutic effect of nomifensine. For this purpose the scores for the relevant items on the Hamilton and Zung Depression Scales were followed up individually (Figure 5).

HVA levels in the cisternal CSF of the five patients responding positively to nomifensine, were investigated separately. It was found that the mean level was significantly lower than the corresponding mean of the non-responding patients, and was also significantly lower than the overall mean of 21 patients (Figure 1; Table 3). This was not true for 5-HIAA levels. This could be taken to indicate that the antidepressant effect of nomifensine is in fact connected with an activation of the central

dopaminergic hypoactivity existing in these patients. Furthermore, the therapeutic effect of nomifensine on the factor 'retardation' was more obvious compared with clomipramine (Figure 5).

In relation to the biochemical investigations, the following should be noted. After 4 weeks' medication γ -GT levels in the blood of three patients treated with nomifensine, were found to exceed 40 units. In one patient from the clomipramine group, the level had increased to over 150 units, and in two cases the level had increased to 51 units. Apart from this there were no significant deviations in the blood chemistry of these patients.

Probenecid levels in the CSF of all patients showed relatively little variation, with a mean level of 16.7 $\mu\text{g/ml}$ and a range of 8–26 $\mu\text{g/ml}$ (Table 1).

Discussion

According to van Praag (1974), it may be possible to introduce biochemical typing into the research of unipolar (endogenous) depression. Central serotonergic and/or central dopaminergic

Table 2 Mean total scores, on Zung and Hamilton Depression Scales, before and after treatment with nomifensine.

	Hamilton		Zung	
	Day 0	Day 28	Day 0	Day 28
Positive response ($n=5$)	30 (27-34)	6 (2-15)	62 (31-79)	44 (24-66)
Non-responders ($n=5$)	32 (24-40)	25 (18-36)	66 (55-74)	64 (54-75)

Table 3 Mean levels of cisternal CSF HVA and 5-HIAA, in responders and non-responders to nomifensine, compared with all patients.

	HVA (ng/ml)	5-HIAA (ng/ml)
Responders ($n=5$)	159.8	90.8
Non-responders ($n=6$)	283.3	142.2
Total patients ($n=21$)	258.7	108.5

hypoactivity may be found in such depression. Tricyclic antidepressives can have a more selective influence on these two monoaminergic systems. For example, clomipramine can activate the central serotonergic system by active blockade of 5-HT re-uptake in the synaptic cleft. According to Coppen *et al.* (1973), there are unipolar depressions in which the tryptophan level in serum and in CSF is lowered. In these patients, serotonergic hypoactivity can perhaps be related to a precursor deficit.

Nomifensine more selectively activates the central dopaminergic system. It can be considered to be a dopaminergic agonist (Costall *et al.*, 1975).

Nomifensine may, as a result of this neuropharmacological activity, be expected to have a therapeutic effect in depression associated with hypoactivity of the central dopaminergic system. According to Korf & van Praag (1971a) and van Praag *et al.* (1973), such hypoactivity may be associated with a typical clinical picture, in which psychomotoric retardation is prominent. In this type of unipolar depression the retardation is sometimes more obvious than the disturbance of mood itself. In contrast (Goodwin *et al.*, 1973), serotonergic hypoactivity can be more related to the depressed mood.

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Discussion

DR ECCLESTON (Edinburgh) asked whether there were significant between group differences in

probenecid blocks the efflux of the acid metabolites of the cerebral monoamines from the CNS to the blood stream. The mean levels of these metabolites, HVA and 5-HIAA are higher in cisternal liquor than in lumbar CSF. Changes in these metabolites may more obviously be determined therefore in cisternal CSF.

In this study a better therapeutic effect with nomifensine was observed in patients in whom a diminished turnover of DA was determined using the probenecid technique.

Nomifensine showed also a better therapeutic effect than clomipramine on the factor 'retardation' in the Hamilton Depression Scale.

In conclusion, biochemical screening of patients with unipolar endogenous depression using the probenecid technique can be useful. It could perhaps enable more selectively acting antidepressants to be used to interfere selectively with the central serotonergic or the central dopaminergic system.

Patients with so-called 'retarded' unipolar depression would benefit more from an antidepressant with a predominantly DA potentiating action.

probenecid levels, or whether there was a correlation between 5-HIAA and probenecid.