A NEW ADJUNCT TO THE TREATMENT AND MANAGEMENT OF DEPRESSION: INTRAVENOUS INFUSION OF CHLORIMIPRAMINE (ANAFRANIL)*

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The two psychiatric inpatient units at Johannesburg Hospital together handle about 1 000 patients annually. These units cater to a population of about 600 000 people and are involved in the investigation, treatment, management and disposal of patients who are psychiatrically ill as well as psychiatric emergencies. This service is in addition to the already extensive outpatient facilities at Johannesburg Hospital as well as the Tara Neuro-Psychiatric Hospital for long-term therapy.

METHOD AND MATERIAL

The aims of the present investigation were to estimate the effects of intravenous chlorimipramine therapy and to compare, if possible, the results obtained by electroconvulsive therapy (ECT). Because of practical difficulties it was not possible to do a double-blind study comparing intravenous infusion against electroconvulsive shock. In addition to the major study, a group of inpatients treated with conventional antidepressant drugs were compared with the other two groups.

A total of 438 patients were studied during 1967 - 1970 and the chlorimipramine group were investigated between June 1968 and May 1970. One group comprised 352 inpatients of whom 58 received ECT (21 males, 37 females), 255 conventional antidepressant therapy and 39 intravenous chlorimipramine (7 males, 32 females). In addition, there were 86 outpatients of whom 31 were treated with ECT (13 males, 18 females) and 55 with infusion of chlorimipramine (21 males, 34 females).

Ages of patients ranged from under 20 to over 60 years with slightly more cases in the 21 - 30, 41 - 50 and 51 - 60 decades. There were, however, no significant differences between the two groups.

Parameters studied included the period in hospital and number of days off work, number of treatments required, response to therapy, and side-effects. In order to compare the ECT and chlorimipramine groups patients were paired for sequential analysis according to sex, age (within 5 years) and, wherever possible, severity of symptoms. Data were scored as indicated in Table I.

TABLE I. SCORING OF DATA

Number of treatments needed for improvement:					
Number of treatments	*12+*	*10 - 12*	*7 - 9*	*4 - 6*	*1 - 3*
Score	0	1	2	3	4
Days before return to work or off work:					
Days before working*	*15+*	*11 - 15*	*6 - 10*	*1 - 5*	
Score	0	1	2	3	
Side-effects other than confusion:					
	Severe	*Mild*	*None*		
Score	0	1	2		
Response to treatment:		*Sums of scores*			
Moderate - excellent		7 - 9			
Slight - moderate		4 - 6			
Indifferent		1 - 3			
Poor		0			

*Many patients, especially on intravenous ch'orimipramine, went to work after treatment in the morning and were assumed to have half a day taken off for each day of treatment.

This method of scoring for response to treatment gives most weight to the number of treatments (a possible 4 out of 9, i.e. 44%) and days off work (a possible 3 out of 9, i.e. 33%). Factors such as side-effects had a low weighting (2 out of 9, i.e. 22%).

Selection of Cases

Ten criteria of depression were chosen, viz.:

1. Depression including attempted suicide and suicidal ideas.
2. Psychological and psychomotor retardation, including poor concentration and falling-off of work performance.
3. Terminal insomnia.
4. Diurnal variation of mood.
5. Loss of weight.
6. Guilt.
7. Hypochondriasis.
8. Loss of libido and amenorrhoea.
9. Agitation.
10. Previous history.

Only patients who presented 5 or more of these criteria were considered in the study and at least 2 of the first 5 criteria were present in every case.

Technique of Chlorimipramine Infusion

Initially 1 ampoule of chlorimipramine 25 mg in 250 mg of 5% dextrose saline was administered intravenously at the rate of 60 drops per minute. The duration of the drip was 1 - 2 hours. With increasing experience and confidence intravenous infusions of 50 - 100 mg were given. Later, for economy reasons, 25 mg of the drug in 150 ml dextrose saline was given at 25 - 30 drops per minute. However, it was found that when larger doses of the drug were given, particularly 75 - 100 mg, the tendency to local venous thrombosis increased and the higher doses were subsequently given in 250 or 500 ml of dextrose saline. The small vessels of the hand and forearm were used.

Associated Therapy

Doses of oral chlorimipramine 25 mg *b.d.* or *t.d.s.* were continued when intravenous therapy had been stopped. It had been the rule in these units to continue antidepressant oral drug therapy on discharge for 3 - 12 months as outpatients. The follow-up at outpatient level is usually 66 - 75% for the first 2 years. In addition to psychotherapy, especially in the early stages, a minor or major tranquillizer or a minor antidepressant was often instituted. Occupational therapy and adjunct treatments were given when necessary. For the purpose of this trial, however, only the intravenous therapy phase was studied and concomitant treatment was kept constant as far as possible.

RESULTS

From a clinical point of view, the most notable effect of intravenous chlorimipramine was the rapid response to treatment. There was an improvement of more than 50%

*Date received: 5 November 1970.

3 treatments or within 10 days in which these treat- were given. The avoidance of anaesthetic and the able post-ECT confusion as well as the readiness tivity after the intravenous treatment proved to be important advantages for the new form of therapy. responsibility of the therapeutic team was to get ts out of hospital and back to work; after the first ıths of the study approximately 75% of the patients being treated as outpatients so that there was no to admit them to hospital and, in addition, they go back to work on the same day after the infusion ›y.

ffects of Infusion Therapy

ating, drowsiness, mild dizziness and sinus tachy- occurred very commonly, but these effects did not b the patients. At least half the patients would for $\frac{1}{2}$ - 1 hour after the treatment and for longer ls with higher doses, and the reactions always l off without any severe after-effects. Blood pressure ıot significantly affected in any of the cases. No ic reactions were noted. In fact, throughout the the complications were notable by their absence. pyramidal symptoms occurred in 3 patients, all fe-, only one of which was severe enough to necessitate ıtinuing treatment; this patient had developed severe ›yramidal symptoms on all the antidepressive drugs ›usly tried. The two mild cases of parkinsonism nded easily to antiparkinsonian drugs and treatment ıot discontinued. Local venous thrombosis occurred patients, 3 females and 1 male, to the extent that required hot fomentations and inunction of local in or hyaluronidase. At no stage did the phlebo-ıbosis require cessation of treatment.

e case developed congestive cardiac failure and py was discontinued although it was felt that this ınrelated to the treatment. Nevertheless, in the final this case was assessed as being a failure with serious ffects.

tical Evaluation of Data

hi-squared test was applied to the data to test if the ences were significant between the proportion of ıts in hospital who improved using the three different nents, viz. ECT, antidepressant drug and intravenous ion of chorimipramine. This proved to be so, for nale and female patients combined, at the 2% level gnificance.

e central limit theorem was used to test the difference he two treatments ECT and intravenous infusion of imipramine), between the mean numbers of treat-s, and between the mean numbers of days off work. e U-statistic

$$U = \frac{\overline{X}_1 - \overline{X}_2}{\sqrt{\frac{S_1^2}{N_1} + \frac{S_2^2}{N_2}}}$$

used to test the difference between the total mean s. U- calculated will have an approximate normal one distribution under the nul hypothesis of no ence. The difference between the mean number of nents gave a U-value of 3·92. This is significant (in favour of chlorimipramine) at the 0·01% level of significance (i.e. less than 1 chance in 10 000 of obtaining this result by chance alone).

The average number of treatments for patients having ECT was 6·67 ± 0·80 whereas the average for patients on intravenous infusion of chlorimipramine was 4·71 ± 0·58. Sequential control charts were constructed in order to

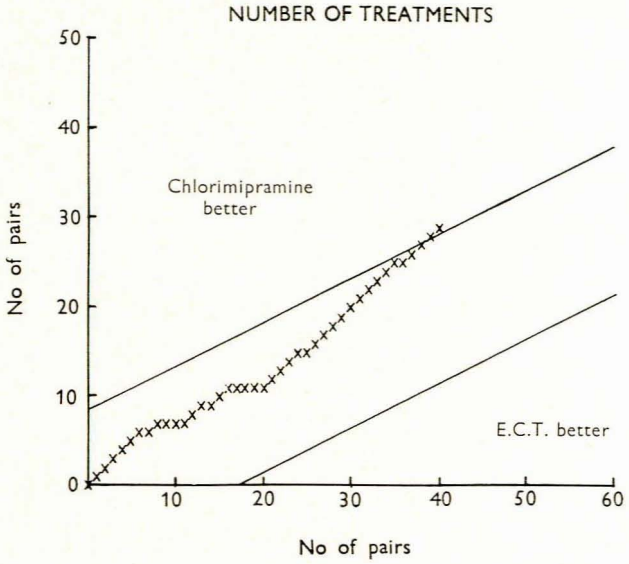

Fig. 1. Number of treatments with ECT compared with chlorimipramine therapy.

illustrate these results diagrammatically and the breakthrough with regard to the number of treatments occurred at a preassigned significance level of P = 0·001 (Fig. 1).

The difference between the mean number of days off work gave a U-value of 11·49. This is a highly significant result, so much so that a value of 11·49 is not tabulated.

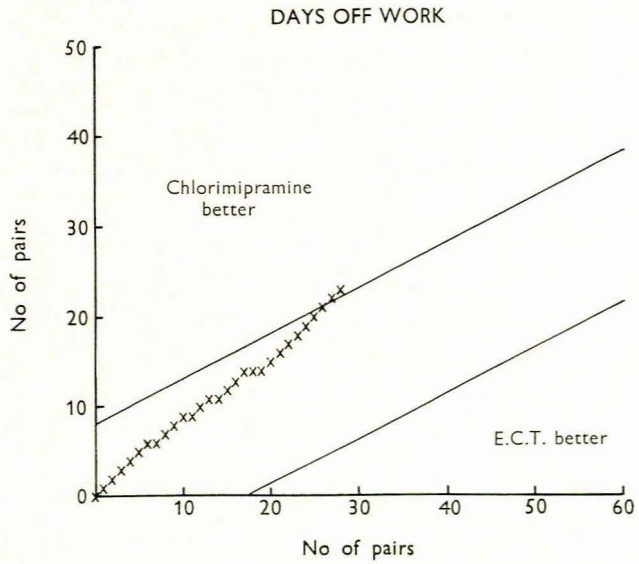

Fig. 2. Number of days off work in patients on ECT compared with chlorimipramine therapy.

There is less than 1 chance in 10 000 of obtaining a result as large as this by chance alone. The average number of days off work for a patient having ECT was 32 (32·30 ± 1·71), whereas for chlorimipramine it was only 9 days, i.e. (8·98 ± 1·10). A roughly linear relationship was found between the number of treatments for patients on ECT and the number of days off work. This is not true when a patient is on chlorimipramine where the maximum number of days off work was 30. This may not, however, be due to the effect of treatment, but rather to the method of application. A sequential control chart again showed a breakthrough at a preassigned significance level of $p = 0{\cdot}001$ in favour of chlorimipramine (Fig. 2).

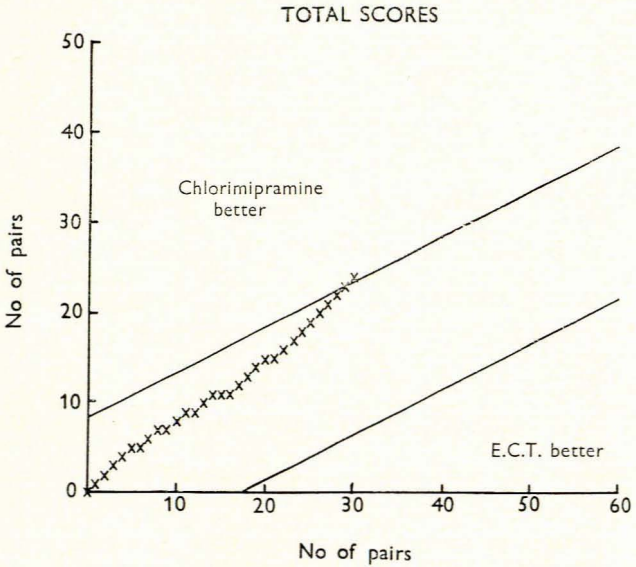

Fig. 3. Total scores.

This mean difference between the total scores was significant at the 1% level of significance in favour of chlorimipramine (Fig. 3).

The equations of the lines for sequential analyses used were:

$$Y_1 = -8{\cdot}5168 + 0{\cdot}4997X$$
$$Y_2 = +8{\cdot}5168 + 0{\cdot}4997X$$

for X = 0	$Y_1 = -8{\cdot}5168$	$Y_2 = +8{\cdot}5168$
17	= 0	
30	= 6·5	
60	= 21·5	= 38·5

SUMMARY AND CONCLUSIONS

The difference between the proportion of patients in hospital who improved when treated with electroconvulsive therapy, conventional antidepressant drug therapy and intravenous infusion of chlorimipramine was statistically significant in favour of the last-mentioned treatment. Patients on chlorimipramine as a group needed fewer treatments and returned to work more rapidly than did their counterparts having electroconvulsive therapy. There were no side-effects other than confusion in patients having electroconvulsive therapy while several on the infusion suffered from mild side-effects. One patient developed congestive cardiac failure. This was thought to be due to other causes but was assessed as being due to the infusion.

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