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CLOTIAPINE IN THE MANAGEMENT OF ALCOHOLISM AND DRUG ADDICTION

REPORT ON A CLINICAL TRIAL

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SUMMARY

The management of withdrawal symptoms in chronic ethanol and drug addiction is a complex problem, requiring an intensive search for new drugs with greater therapeutic and minimal side effects.

We had the opportunity to assess in an open, uncontrolled clinical trial Clotiapine (Etomine ®, Wander), which is a chemically new tricyclic substance, a dibenzothiasepine.[1-6] The intensive sedative action of Etomine has an immediate effect (particularly by the intravenous route) on agitation, anxiety, restlessness and tension commonly found in alcoholism and states of confusion.[7-9] Etomine is well tolerated by the patients.[10]

Of the 101 adult in-patients included in this trial at the Castle Carey Clinic, 82 were chronic alcoholics, 7 drug addicts and 12 addicted to both alcohol and drugs. They were treated with Clotiapine. The overall response (very good or good) rate or daily clinical observations was 96%. Side effects were rarely observed.

In this trial it has been demonstrated that Clotiapine is an effective drug for the treatment of alcoholism and drug addiction.

SELECTION OF PATIENTS

All new admissions to the hospital during the trial period, with symptoms of severe intoxication, were included in this trial and treated from the outset with Etomine. Alcohol and drugs of addiction were completely withdrawn at the commencement of Etomine therapy.

MATERIAL AND METHOD

Etomine was administered by the parenteral and/or oral routes. The pharmaceutical preparations used were:

TABLE 1: MAXIMAL DAILY DOSAGE
(1 Unit = 1 ampoule or 1 tablet of 40 mg)

Route of Administration	*Group*	*Number of Units per Day* 1	2	3	4	5	6	7	8	9	10+	*Total*
Intravenous	1	2	10	24	1	1				1		39
	2		1		2			1				4
	3		1	4								5
Intramuscular	1	3	7	9	22	22	9	4	5	1		82
	2	1	1			1	2	1			1	7
	3		1	2	3	2	2	1			1	12
Oral	1		1	6	17	31	22	4	1			82
	2			2		2	2				1	7
	3			2	3	1	3	2	1			12

1. Ampoules containing 40 mg per 4 ml solvent:
   (a) For intravenous use;
   (b) For intramuscular use.
2. Tablets of 40 mg for oral use.

Forty-seven patients received an average daily dosage of 80-160 mg intravenously for several days. Subsequently, Etomine was administered intramuscularly for a further one or two days and continued by the oral route at a daily dosage of 80-240 mg or more; fifty-four patients were started on Etomine intramuscularly and after 4-6 days received the drug orally. Dosage was gradually tapered off until a daily maintenance dosage of 10-40 mg (rarely 80 mg) was reached.

The patients were examined daily. A rating scale of 0-4 was used for each of these symptoms:

1. Anxiety
2. Agitation
3. Aggressiveness
4. Disorientation
5. Hallucinations
6. Paranoid delusions
7. Insomnia
8. Difficulty in social contact
9. Memory disorders
10. Tremor
11. Depression

Simultaneously, the patients' blood pressure and pulse rate were checked and side effects noted on individual patient records.

No other psychotropic agents were used during the trial.

TRIAL POPULATION

This consisted of 3 distinct groups of hospitalized patients suffering from:

1. Alcoholism: 82 patients;
2. Drug Addiction: 7 patients;
3. Alcoholism plus drug addiction: 12 patients.

The drugs of abuse fall into 5 main groups.

1. Narcotics: Pethidine, Morphine, Heroin;
2. Stimulants: Amphetamine, Cocaine;
3. Sedatives: (a) Barbiturates;
   (b) Non-Barbiturates.
4. Tranquillizers.
5. Hallucinogens: LSD, Marihuana.

The age groups and sex were as shown in Table 2.

At the end of the trial each patient was placed in one of 4 categories (very good; good; poor; no effect). The assessment was made according to the investigator's general impression of therapeutic response.

DISCUSSION

Table 3 indicates that the overall therapeutic results were remarkable, considering that most of the addictions were of long standing; 96% of all patients and 97% of the 82 chronic alcoholics in this trial showed a very good or good response. In addition, over 300 other non-trial patients have undergone similar therapy at the same clinic with similar results.

Etomine showed very satisfactory results in the treatment of drug addiction (100% response). Many of these patients were hard cases of addiction, having been using several drugs simultaneously over many years. Almost all of them were so-called 'mainliners'.

Only one patient did not respond as well as the others. She was a young woman of 23 who started taking drugs such as morphine, barbiturates, amphetamines, LSD, cocaine and heroin at the age of 14. After one month of

TABLE 2: AGE GROUPS AND SEX

Sex	*Group*	*Less than* 10	11–20	21–30	31–40	41–50	*Over* 51	*Total*
Male	1		7	13	25	14	5	64
	2				1			1
	3	1	1	3	2			7
								72
Female	1			4	8	5	1	18
	2		1	4			1	6
	3		1	4				5
								29
Total		1	10	28	36	19	7	101

TABLE 3: OVERALL RESPONSE

Group	*Diagnosis*	*Very Good*	*Good*	*Poor*	*No Effect*
1	Alcoholism	73%	24%	3%	—
2	Drug addiction	57%	43%	0%	—
3	Alcoholism + drug addiction . .	84%	8%	8%	—

TABLE 4: GROUP 1: ALCOHOLICS

Day of Observation	0		1		2		3		4		5		6		7		8		9		10		11		12		13	
Number of Patients	82		82		82		82		81		81		81		80		80		80		80		80		80		80	
Symptoms	*Patients with Symptoms*	*Total Score*	*Patients with Symptoms*	*Total Score*	*Patients with Symptoms*	*Total Score*	*Patients with Symptoms*	*Total Score*	*Patients with Symptoms*	*Total Score*	*Patients with Symptoms*	*Total Score*	*Patients with Symptoms*	*Total Score*	*Patients with Symptoms*	*Total Score*	*Patients with Symptoms*	*Total Score*	*Patients with Symptoms*	*Total Score*	*Patients with Symptoms*	*Total Score*	*Patients with Symptoms*	*Total Score*	*Patients with Symptoms*	*Total Score*	*Patients with Symptoms*	*Total Score*
Anxiety	78	211	74	139	64	105	47	81	38	60	29	42	15	20	7	10	4	4	1	1	1	1	1	1	1	2	1	2
Agitation	51	111	42	60	32	49	19	56	12	22	7	13	4	11	3	3	—	—	1	1	—	—	—	—	—	—	1	2
Aggressiveness	22	45	14	16	14	26	12	26	9	14	4	6	3	4														
Disorientation	46	76	26	32	23	50	19	43	20	32	12	16	6	7	1	1	1	1	2	2	1	1						
Hallucinations	12	19	8	12	17	39	16	31	13	21	5	6	2	2	1	1	1	1	1	1	1	1	1	1				
Paranoid delusions	3	6	2	2																								
Insomnia	38	51	26	30	25	41	27	42	23	28	14	17	6	9	7	10	5	6	2	3	2	3	2	3	3	3	1	1
Difficulty in social contact	48	74	27	31	18	30	14	26	12	15	6	7	2	2	1	1	1	1										
Memory disorders	34	52	17	21	17	33	15	30	14	20	5	7	3	4	2	2	1	1	2	2								
Depression	4	12	5	13	5	11	8	16	8	11	3	4	2	2	2	3	2	2	1	1	1	1	1	1	1	1	1	1
Tremor	5	14	8	23	9	19	11	21	12	23	9	17	7	11	5	6	3	4	2	3	2	2	2	2	2	2	2	2

treatment her residual symptoms were anxiety, agitation, aggressiveness and insomnia. With Etomine no severe withdrawal symptoms occurred.

Our biggest success in this group was the management of two LSD addicts, both showing severe psychotic symptoms. Both of them are completely recovered and have been off all drugs of addiction for more than a year.

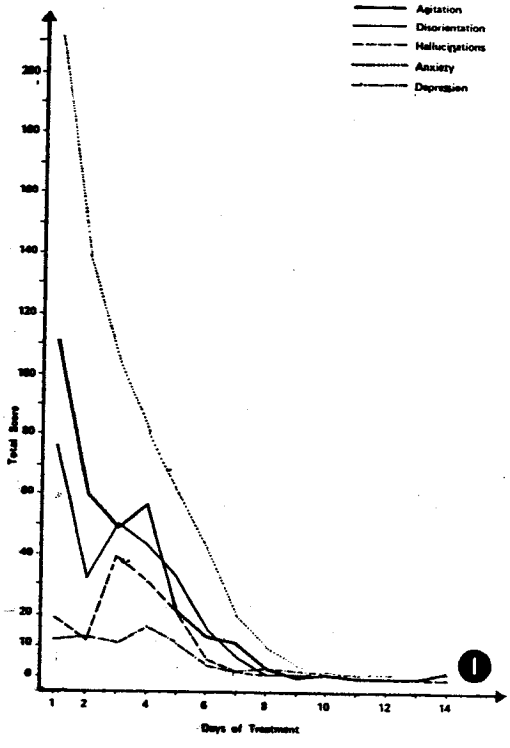
GENERAL TOLERANCE AND SIDE EFFECTS

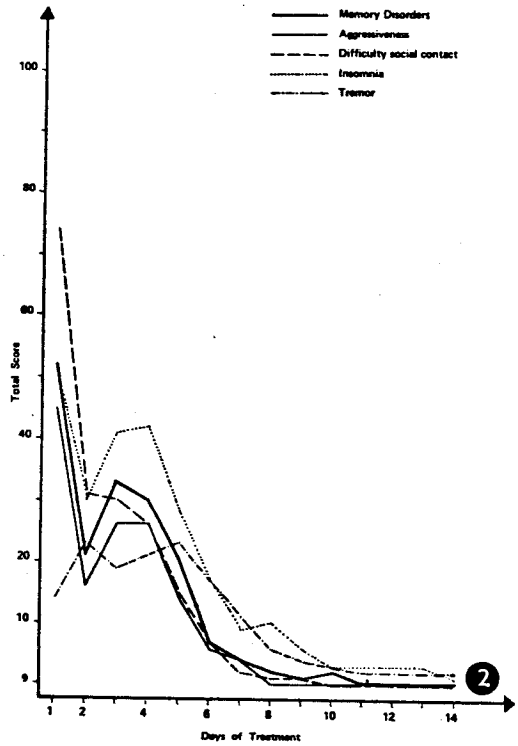
Etomine was well tolerated by patients of all 3 groups. It had hardly any adverse effects on the cardiovascular system. No abrupt changes in pulse rate or blood pressure were observed during this study.[10] Whenever feasible, the intravenous injection was given slowly. A sudden blood pressure drop has not been observed.[10] Etomine in high doses (500-600 mg per day) was given for a few days only and this may explain the lack of extrapyramidal side effects.

Vegetative and gastro-intestinal side effects rarely occurred.

Three cases of delirium tremens were terminated by the intravenous administration of Etomine; three patients had a transient worsening of the tremor (lasting 6-8 days).

Depression of 2 patients became temporarily worse for 8-10 days, but improved rapidly afterwards.





In addition a highly interesting observation was made. Chain smokers seemed to smoke considerably less during Etomine therapy. The craving for tobacco was attenuated. Tobacco smoke tasted bitter and left a bitter aftertaste.

CONCLUSION

On the basis of our experience with this trial, we conclude:

(a) The best schedule for Etomine administration is as follows:

Commence with the intravenous route at relatively high dosage depending upon:

1. The degree of intoxication; and
2. The general physical condition of the patient.

The intravenous dosage must, therefore, be reviewed daily.

After 2-3 days, Etomine can be given intramuscularly and/or orally. On discharge the patient is placed on a maintenance therapy of 10-40 mg per day.

(b) In view of the rapid rate of resolution of withdrawal symptoms and in view of its good tolerance, Etomine can be prescribed in all cases of toxicomania. The treated patient can be reintegrated quickly into community life, thus contributing towards a solution of this grave social problem.

(c) Etomine reduces the craving for tobacco smoking. This aspect should be investigated further.

Figs. 1 and 2 and Table 4 illustrate the chronological improvement of the target symptoms.

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DESAMINO OXYTOCIN (SANDOPART) AND PITOCIN IN THE INDUCTION OF LABOUR

A COMPARATIVE TRIAL

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SUMMARY

In a trial of desamino oxytocin (Sandopart) and pitocin by intravenous infusion combined with amniotomy as a method of inducing labour, Sandopart ensured a shorter induction delivery interval in both nulliparous and multiparous patients.

Vaginal delivery occurred in 97% within 18 hours and in 90% within 12 hours respectively.

Compared with patients in whom onset of labour was spontaneous, maternal and foetal complications were minimal in the trial patients.

The hazards of intravenous oxytocics should be borne in mind and supervision of the patients must be meticulous. The same precautions are required as for intravenous administration of other oxytocics.

In this series, the overall duration of labour was considerably shorter than stated by other authors. Intravenous infusion of Sandopart to induce labour proved to be slightly superior to pitocin in this trial.

INTRODUCTION

The value of oxytocin and pitocin as oxytocics is well documented. In 1960 Du Vigneaud and his associates concluded that a safe and reliable oxytocic could be developed with Sandopart. In Sandopart (a derivative of oxytocin), the amino group in the half cystine residue is replaced by a hydrogen ion, yielding a highly potent analogue of oxytocin, which can be administered orally or by intravenous infusion. It is readily absorbed and is not destroyed by oxytocinase. It has a powerful stimulant effect on the pregnant human uterus.

By amniotomy and simultaneous intravenous infusion of Sandopart or pitocin, the induction delivery interval was shorter when compared with pitocin and spontaneous onset of labour. The incidence of failed induction