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Piracetam and Chlormethiazole in Acute Alcohol Withdrawal: A Controlled Clinical Trial.

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Sixty in-patient alcoholics, presenting with an alcohol withdrawal syndrome after at least one week's drinking bout, were randomly allocated to fixed dose regimens of either piracetam or chlormethiazole in a one-week double-blind trial.

The patients were studied in respect to physical and biochemical parameters as well as symptom reduction and side-effects.

The battery of rating scales demonstrated a good symptom reduction in both drug groups. On the whole a small tendency to more symptom items being reduced on piracetam in comparison with chlormethiazole was found. But the three items, sleep disturbances, decreased libido at the initial phase, and the staff's assessment showed statistically significant differences in favour of chlormethiazole.

This study demonstrated that piracetam was just as efficient as chlormethiazole in patients not requiring sedation.

Introduction

Chlormethiazole has grown more and more popular in some countries because of its high symptom reduction efficacy in alcohol withdrawal states. It has sedative as well as anti-convulsive properties. The risks for addiction however are apparent and the craving for further administration is often observed in alcoholics. Alternatives to chlormethiazole in acute alcohol withdrawal states may therefore be of interest.

Piracetam (2-oxo-pyrrolidine-acetamide) is a simple compound, chemically related to GABA. Animal studies have shown that piracetam facilitates monosynaptic cortical evoked potentials (Bures & Buresova 1968, Dimond 1975, Giurgea & Moyersoons 1970, Giurgea *et al* 1972), improves learning in alcoholic rats (Giurgea & Mouravieff-Lesuisse 1972), and increases the energy reserves in, and the resistance to, hypoxia by the cerebral cell (Giurgea *et al* 1970, Lagergren & Levander 1974). In man it has no sedative or stimulating effects and a very low range and incidence of side-effects.

Double-blind studies using piracetam have been performed in alcohol withdrawal states. The preferences of piracetam in comparison

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with placebo (Petty 1973, Knott & Beard 1973), dixyrazine (Weckroth & Mikkonen 1972), and chlorpromazine (Marks 1976) have been reported. However there is a report by Ahlfors, Hussi and Kyander (1973) showing no differences between the effects of piracetam and placebo as well as dixyrazine.

The purpose of this study was to make a double-blind comparison between piracetam and chlormethiazole during one week's fixed administration in acute alcohol withdrawal.

Patients and Methods

1. *Design*

In-patients (age range 25–55 years) were selected and randomly allocated to either piracetam or chlormethiazole for one week's medication. Only patients with the diagnosis "chronic alcoholism" and a previous history of at least 10 years alcohol abuse were accepted. When entering the investigation the patients had been drinking for at least 7 days and were clinically in an acute alcohol withdrawal state. Patients with a history of heavy drug addiction were excluded.

Following a screening interview to ensure adherence to the inclusion criteria, individual patients were admitted to the trial on their first morning in hospital, having arrived in hospital the evening or night before. From arrival to inclusion in the trial, the patients were only permitted chloral hydrate up to 1 g *in toto*. The patients were treated on the same ward during the trial period and were not allowed to leave the ward without the company of a nurse. Specific nursing personnel were appointed for this purpose.

Before entering the study, informed consent was given by each patient.

2. *Drug administration*

- Piracetam, 4·8 g divided into 3 daily intakes of 2 tablets at 800 mg.
- Chlormethiazole, according to the following table; each capsule to contain 0·3 g chlormethiazole.

Day	*Morning*	*Noon*	*Afternoon*	*Evening*
1	2	2	2	3
2	2	2	2	3
3	1	2	2	3
4	1	1	2	2
5	1	1	1	2
6	0	0	1	2
7	0	0	0	2

Thus patients received either chlormethiazole, caps. 0·3 g according to the schedule plus 2 tablets placebo (identical in appearance to Piracetam), t.i.d.

OR

2 tablets Piracetam at 800 mg t.i.d. (4·8 g) plus placebo (identical in appearance to chlormethiazole) according to the schedule.

No other psycho-active drugs were administered during the trial.

3. *Patients*

Sixty patients, all males except one, completed the trial. Thirty-two patients were treated with piracetam and twenty-eight with chlormethiazole, the mean age in the groups being 39 and 37 years respectively.

The patients were studied with Evenson's "Alcohol History Manual" to collect background data. Of the total trial population, 45·9% had had delirium tremens and 33·0% had abused drugs on at least one occasion. No significant differences were found between the two test groups.

The daily amount of alcohol in the two groups during the last week before entering the trial was 150–450 g. Again no statistically significant difference was found between the groups.

Three patients dropped out of the trial:
- one due to chlormethiazole oversensitivity,
- one patient on piracetam had an epileptic seizure, and
- the other could not accept the medication due to a gastric ulcer.

4. *Assessment methods*

(a) *Physical,* including *neurological examination:* Days 1 and 7.

(b) *Laboratory examination* of blood and urine, 24 items: Days 1, 3, 5 and 8.

(c) *Background information:*
  (1) the SRB part of the DS-battery (Dureman, Kebbon & Östberg 1971);
  (2) the Revised Visual Retention Test (Benton 1974), and
  (3) the Alcohol History Form (Evenson 1975), on Day 6 or 7.

(d) *Test procedures:*
  (1) Comprehensive Psychiatric Rating

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Scale (CPRS) (Montgomery *et al* 1976) on Days 1 and 7.
(2) Clinical Side-Effect Scale (CSE) (Andersen *et al* 1974) daily.
(3) Adjective Check-List (ACL) (Hartvig-Ericsson & Takac 1973) daily.
(4) Daily Estimation Scale (DES) (Carlsson & Wilhelmson 1977) daily.
(5) Tremormeter recordings daily, and
(6) Memory Test (Cronholm & Schalling 1965) on Days 1 and 7.

All the ratings were performed by two psychologists who had demonstrated good inter-rater reliability values.

The psychologists did not communicate with the nursing staff about the patients, except for the DES which scale was also used by the nursing staff, in order to avoid receiving any possible information about the clinical response to the two drugs.

5. *Statistical methods*

Statistical significance of differences between uncorrelated and correlated means (Ferguson 1959, Guilford 1973), and differences between uncorrelated proportions and between frequencies (Hald 1952) were performed. Different items have been correlated against each other (Ahlström 1971).

Results

The data accumulated is extensive and only some of it will be commented on. The reader is referred to an unpublished paper for more detailed data (Carlsson & Wilhelmson 1977).

Epilepsy occurred in one patient who dropped out. No significant differences could be observed between the two groups in respect to blood and urinary examinations.

Test results are presented in Tables 1 and 2. Improvement during the week of trial was reported in 90·4% and 88·7% of the items in

Table 1

Comparison of test procedure results (means) between 1st testing session (pre-drug) and final testing (Day 7) in patients receiving piracetam

	Means		$z-$ *Values*
	1st day	*7th day*	
Comprehensive Psychiatric Rating Scale (estimation range 0–3)			
Depressive thoughts	1·40	0·77	+ 3·41***
Fatigue and loss of initiative	1·86	0·81	+ 6·6 ***
Difficulty in concentration	1·36	0·67	+ 4·33***
Sleep disturbances	2·42	1·77	+ 2·25*
Vegetative disorders (reported)	1·59	1·14	+ 2·22*
Muscular tension (reported)	1·23	0·81	+ 1·86
Decreased libido	1·54	1·04	+ 2·06*
Adjective Check-list			
Anxiety (estimation range 0–22)	3·77	1·75	+ 2·18*
Anxiety/depression (estimation range 0–30)	7·60	2·28	+ 4·61***
Tremormeter recordings			
Tremor registration	118·81	55·03	+ 5·79***
Time of error	148·03	63·35	+ 5·77***
Clinical Side-Effect Scale (estimation range 0–4)			
Nausea	1·94	0·16	+ 6·72***

$p < 0·05$ *
$p < 0·01$ **
$p < 0·001$ ***

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Table 2

Comparison of test procedure results (means) between 1st testing session (pre-drug) and final testing (Day 7) in patients receiving chlormethiazole

	Means		*z − Values*
	1st day	*7th day*	
Comprehensive Psychiatric Rating Scale (estimation range 0–3)			
Depressive thoughts	1·34	0·95	+ 2·47*
Fatigue and loss of initiative	2·00	0·68	+ 8·78***
Difficulty in concentration	1·39	0·84	+ 6·54***
Sleep disturbances	2·44	0·88	+ 6·85***
Vegetative disorders (reported)	1·75	1·05	+ 2·96**
Muscular tension (reported)	1·45	1·05	+ 2·12*
Decreased libido	1·87	0·37	+ 4·95***
Adjective Check-List			
Anxiety (estimation range 0–22)	3·86	1·64	+ 3·57***
Anxiety/depression (estimation range 0–30)	8·46	3·00	+ 4·78***
Tremormeter recordings			
Tremor registration	90·04	51·29	+ 4·43***
Time of error	102·70	53·11	+ 4·15***
Clinical Side-Effect Scale (estimation range 0–4)			
Nausea	1·18	0·36	+ 3·5***

$p < 0{\cdot}05$ *
$p < 0{\cdot}01$ **
$p < 0{\cdot}001$***

the patients who were treated with piracetam and chlormethiazole respectively. The improvement was statistically significant at the 5% level in 70·4% and 67·6% of the items in the two groups studied.

There were no significant differences between the two groups, except for sleep disturbances, libido and the ward-staff's assessment (DES). The piracetam patients had more marked sleep disturbances during the first three nights (Figure 1) in comparison with those receiving chlormethiazole. Decreased libido was reported in both groups but the reduction remained longer in the piracetam patients. The nurses rated the piracetam patients to be more tense and worried during the first three days but not thereafter. No major side-effects of either piracetam or chlormethiazole were found.

Discussion

The patients included in both groups can be considered to be representative for Swedish alcoholics in a withdrawal state. The period of drinking was at least one week and no patient was considered to be in a pre-deliric state. These patients cannot therefore be considered as alcoholics in a very severe withdrawal phase. Normally such alcoholics can be treated without drugs after about one week's stay in the hospital. After 3–5 days' hospital care, they usually ask for out-patient care or home visits. Such excursions are, of course, often connected with alcohol or drug intake. In this respect the investigation situation was completely under control by using a nurse as a whole-time contact person. Before the start of the trial, the nurse and the patient discussed all details of the study. The three drop-outs were

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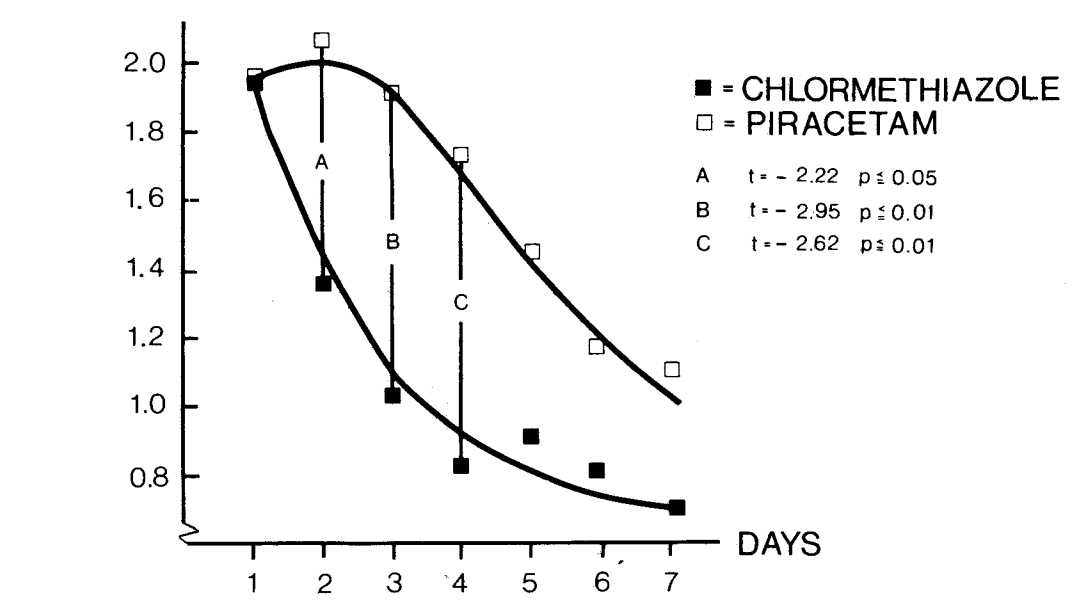

Fig 1 *Sleep disturbances (CPRS scoring) in the piracetam and chlormethiazole patients. The differences between the drugs during the first three nights (A, B, C) are statistically significant.*

due to medical reasons and no patient broke his part of the contract.

On the other hand, the structured investigation programme can influence the results in the two experimental groups. Only 45% of a control group with the same background as our two groups, receiving standard treatment in another department (Carlsson & Wilhelmson 1977) stayed for one week's treatment. Most of the patients in this control group left the hospital when the worst symptoms had disappeared. The patients in our two experimental groups could be motivated to one week's treatment apparently because of a more favourable environment than that on an ordinary ward. That fact may influence the results of recovery but not the comparison between the two drugs.

The symptom reduction was obvious in both experimental groups. Only three items showed statistically significant differences demonstrating less symptom reduction in the piracetam group. One of these may in certain patients be of importance, viz. disturbed sleep. In this respect piracetam is inferior to chlormethiazole in those who initially need sedation. The responsible nurse, however, could not distinguish which drug was used and she was not able to recognize the differences in sedation. Thus no correlation between the nurse's guessing of which drug the patients received and the actual drug was found.

In two patients in the piracetam and one in the chlormethiazole groups, psychotic symptoms and/or a pre-deliric state appeared. Due to the design however we cannot discuss the efficacy of piracetam in pre- and/or deliric states.

Based on the data presented, it can be stated that piracetam is just as efficient as chlormethiazole in reducing abstinence symptoms in non-severe alcohol withdrawal states. Piracetam's lack of any sedative properties may mean that it is not the sole drug to be used in anxious and tense patients with sleep disturbances. However, in other cases the absence of sedation may make piracetam preferable to other traditional therapies.

No differences were found between the two drugs with regard to side-effects.

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