CHLORMETHIAZOLE (HEMINEVRIN) IN THE TREATMENT
OF ALCOHOL WITHDRAWAL

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In the treatment of alcoholic withdrawal symptoms, various tranquilizing drugs have been considered to be more or less effective. The literature on the effects of psychopharmacological agents used for this condition is now almost beyond survey. Controlled drug trials have recently been carried out in the hope that they might provide some scientific basis for treatment. Those commonly used drugs which had been tested were meprobamate, phenothiazine, and benzodiazepine derivatives (4,9,13,14). However, Glatt (1959) carried out controlled trials with several agents, chlorpromazine, promazine, reserpine and found that their effect was not significantly better statistically than that of the placebo. Because of the variety of drugs in use, the lack of adequately controlled trials, and the difficult nature of the study material, no conclusive picture of treatment has emerged. Different drugs appear to have specific advantages and disadvantages.

During the last decade, especially in Scandinavia and most parts of Europe, a new agent—chormethiazole (Heminevrin, Hemineurin, Distranurin) had aroused considerable interest in the treatment of alcohol withdrawal and delirium tremens.

Chormethiazole, chemically the ethane disulphonate of 4-methyl-5-β-chlorethyl-thiazole which has a sedative/

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hypnotic and anticonvulsant effect. Chlormethiazole was discovered in 1953 by French research workers (Charonnat et al., 1953) in the course of their studies on shock conditions provoked by the intravenous administration of the vitamin B, (thiamine, aneurin)

Chemically, vitamin B, is built up of a pyrimidine and a thiazole component. (Figure 1)

Figure 1. Vitamin B1 (thiamine, aneurin)

Pyrimidine part
with a shock producing effect

Thiazole part
with an anticonvulsive effect

It was found that the shock producing effect was entirely attributable to the pyrimidine part. The thiazole part, on the other hand, had an anticonvulsive action. Presumably, therefore, the actions of these two structures are normally antagonistic. The pharmacological properties of a number of derivatives of the thiazole part were investigated, and finally chlormethiazole was discovered which possesses the most pronounced sedative and anticonvulsive effects.

Reports on the clinical application of chlormethiazole in psychiatry mainly describe its use in the treatment of delirium tremens and withdrawal symptoms in alcoholism.

Some of the alcohol abstinence symptoms such as tremors, nervousness, tension, hallucinations, tachycardia, and dilated pupils may develop. These may be due to increased activity of the adrenal glands and the sympathetic nervous system. Carlsson and Haggendal
(1967)\(^3\) found that when chlormethiazole was given, the symptoms were mild and the noradrenaline levels were about normal at all times after withdrawal of ethanol.

Salum (1963)\(^{12}\) treated more than 1,000 patients with sequelae for alcohol abuse in Stockholm and reported that chlormethiazole was not only of value in the treatment of derilium tremens but also in the prevention of the outbreak of derilium tremens and similar conditions. She even ventured to state that a patient who develops a delirium in the course of a treatment with chlormethiazole has probably been given an inadequate dosage.

Glatt (1965)\(^7\) carried on a controlled trial in St. Bernard’s Hospital, London, in which chlormethiazole and a placebo were compared in the treatment of withdrawal symptoms of 102 alcoholic patients. A statistically significant difference was found between the active and placebo groups. No serious side-effects were observed. Although it was advocated that the drug should not be given in depression\(^9\). Glatt disagreed with this view and stressed that there was no contraindication for use of the drug. The results of this trial shows that chlormethiazole is a valuable drug in the treatment of withdrawal symptoms in alcoholics, although in view of the problem of dependence it should not be used beyond a limited time.

Harfst et al. (1967)\(^8\) carried on a controlled double-blind trial comparing chlormethiazole, amobarbital, and placebo in 30 patients with acute alcohol withdrawal symptoms admitted to Bangour Village Hospital, West Lothian, Scotland. The effect on pulse rate, blood pressure, sweating, tremors and sleep was investigated separately. The conclusion was that although both chlormethiazole and amobarbital appeared to be adequate in producing sleep and sedation, neither had any special advantage over the other in the treatment of the alcohol withdrawal state.

The clinical application of chlormethiazole in the ambulatory treatment of alcoholics was reported by Asander (1962)\(^2\) based on the treatment of 70 out-patients at the Stadmissionens Alcoholic Polyclinic, Stockholm. That chlormethiazole had obviously proved to be a valuable compound for the initial ambulatory treatment or prevention of the severe withdrawal syndromes. The usual abstinence symptoms rapidly disappeared and the patient become more suitable for continued psychotherapy. He suggested that, in view of the tendency to abuse drugs among patients with addictive problems, the course of treatment should usually not exceed one week.

A further report on over 200 outpatients by the same author (Asander, 1966)\(^1\) confirmed the initial impression.

Rotter (1966)\(^{11}\) treated 71 alcoholic patients in a psychiatric private practice in Austria and concluded that chlormethiazole showed a good effect in the treatment of acute and pathological
alcohol intoxication as well as in pre-delirious patients. Ambulatory treatment of the abstinence syndromes with chlorpromazine shows good results. Experiences reported by other authors on the treatment of delirium tremens can be confirmed.

In the study presented here chlorpromazine was compared with chlorpromazine and diazepam in the treatment of alcohol withdrawal in-patients. Evaluation was made mainly by objective measurements.

METHOD

The subjects consisted of 76 male alcoholics with acute alcohol withdrawal symptoms admitted to the Faculty of Medicine, Siriraj Hospital, Mahidol University, Most had abused alcohol for years; 68 were drinking up to the time of admission and the remaining 8 maintained that they had stopped more than 24 hours previously but were showing withdrawal symptoms on admission. The mean age was 41 years, the youngest was 28, and the oldest was 70.

On admission, personal data, social characteristics, alcohol history, symptoms, and data regarding their clinical condition were recorded. Additional information regarding individual patients, if required, were sought after through the help of a psychiatric social worker.

Routine laboratory investigation together with liver function tests were performed on admission and at the end of therapy.

Blood pressure and pulse rate were recorded daily.

Since a true double-blind trial was impracticable for practical reasons, the drugs were administered alternately. The first patient receiving chlorpromazine, the second chlorpromazine, and the third diazepam, and so on as before. Tablets, containing either 300 milligram of chlorpromazine, 25 milligram of chlorpromazine, or 5 milligram of diazepam, were allocated to patients accordingly.

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Dosage Pattern</th>
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<tbody>
<tr>
<td>pattern of a drug used tablets</td>
<td>Tablets day</td>
</tr>
<tr>
<td>1st night</td>
<td>4</td>
</tr>
<tr>
<td>2nd day</td>
<td>3×3×4</td>
</tr>
<tr>
<td>3rd day</td>
<td>2×2×3</td>
</tr>
<tr>
<td>4th day</td>
<td>1×1×3</td>
</tr>
<tr>
<td>5th day</td>
<td>1×1×2</td>
</tr>
<tr>
<td>6th day</td>
<td>0×1×2</td>
</tr>
<tr>
<td>7th day</td>
<td>0×0×2</td>
</tr>
<tr>
<td>8th day</td>
<td>0×0×1</td>
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<tr>
<td></td>
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</table>
The amount of chlorpromazine and diazepam was chosen in the light of previous experience with the drugs. Since chlorpromazine does not prevent withdrawal fits, then diphenylhydantoin (Dilantin) capsules 100 milligram three times daily were given to those on chlorpromazine if there was a risk. Those who failed to complete the required trial period were not included in this study.

Table 2

<table>
<thead>
<tr>
<th>Drug group</th>
<th>Number of cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chlorpromazine</td>
<td>28</td>
</tr>
<tr>
<td>Diazepam</td>
<td>23</td>
</tr>
<tr>
<td>Total</td>
<td>76</td>
</tr>
</tbody>
</table>

In addition to the allocated drug, vitamin B was administered in all cases.

The presence or absence of abstinence symptoms was assessed daily; each symptom was graded as either mild or severe.

RESULTS

A total of 76 patients were included in the trial. They showed a fairly even distribution among the three drug groups (Table 2).

Listed in Table 3 are the withdrawal symptoms as recorded on admission day. Agitation, insomnia and anorexia were almost invariably present; tremors, paranoid ideas, and headache were quite common; hallucinations, less so. Each one of the subjects reported malaise of some degree. While the total incidence on any given symptoms was more or less the same in the three groups, the figures for more serious symptoms such as hallucinations, paranoid ideas, agitation, nausea and malaise were disproportionately high in the chlorpromazine group. This could be attributed to the tendency of new residents to allocate chlorpromazine to the clinically more severe patients.

Table 3

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Total present with symptoms</th>
<th>Present with pronounced symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Chlorpromazine</td>
<td>Chlorothiazide</td>
</tr>
<tr>
<td>Agitation</td>
<td>100</td>
<td>75</td>
</tr>
<tr>
<td>Insomnia</td>
<td>93</td>
<td>90</td>
</tr>
<tr>
<td>Anorexia</td>
<td>92</td>
<td>70</td>
</tr>
<tr>
<td>Paranoid ideas</td>
<td>67</td>
<td>35</td>
</tr>
<tr>
<td>Tremor</td>
<td>56</td>
<td>15</td>
</tr>
<tr>
<td>Nausea</td>
<td>52</td>
<td>65</td>
</tr>
<tr>
<td>Headache</td>
<td>41</td>
<td>43</td>
</tr>
<tr>
<td>Vomiting</td>
<td>38</td>
<td>45</td>
</tr>
<tr>
<td>Hallucinations</td>
<td>23</td>
<td>5</td>
</tr>
<tr>
<td>Malaise</td>
<td>100</td>
<td>58</td>
</tr>
</tbody>
</table>
The number of patients whose symptoms were all abolished by the third day amounted to 7 of 28 patients in the clomethiazole group, 6 of 25 patients in the diazepam group, and only 3 of 23 patients in the chlorpromazine group.

The therapeutic effects on individual symptoms as evaluated on the third and sixth days of treatment are diagrammatized in Figure 1. Differences were greatest between the clomethiazole and chlorpromazine groups: for insomnia the difference here was highly significant ($P<0.001$), and for agitation almost significant ($0.05>P>0.01$). On statistical comparison of the clomethiazole and diazepam groups, the former tended to show a better effect but there were not statistically significant differences.

On the sixth day very few individual symptoms persisted; only in regard to subjective malaise were intergroup differences recorded. Here, clomethiazole had a better effect than the other drugs, for 22 patients no longer felt malaise, as compared to 12 in the chlorpromazine groups, and 14 in the diazepam group. The differences were almost significant ($0.05>P>0.01$).

Many of the patients had tachycardia on admission, but tended toward normal during the next three days particularly in the clomethiazole group.

Clomethiazole has the advantage of being anticonvulsant, while chlorpromazine may require the addition of an anticonvulsant for the prevention of alcohol withdrawal fits. Besides, chlorpromazine itself is potentially epileptogenic.\(^6\)

No serious side effects were noted. A few of the patients in the clomethiazole group reported spells of sneezing. The absence of major side effects was probably attributable to the low dosage employed. Most patients complained of the smell and taste of the tablets.

The laboratory investigations carried out before and after the trial did not reveal any adverse effect of the drug.

Although the authors have so far noted that no patients in this study became addicted to clomethiazole. However, in view of the possible risk of dependence or marked sedation\(^12\), the drug should be used for a limited time on an in-patient basis.

**SUMMARY**

A clinical trial was conducted on 76 alcoholic in-patients to compare clomethiazole (Heminevrin) – a derivative of vitamin B1, chlorpromazine and diazepam in the treatment of alcohol abstinence syndrome. Although the drugs produced similar effects on the overall clinical conditions of the patients, but the following withdrawal symptoms such as tremor, nervous tension, hallucination and tachycardia were observed to be milder in patients receiving clomethiazole. And thus their ability to cooperate in the treatment had greatly improved. The powerful anti-convulsive, sedative and hypnotic properties of
chlordiazepoxide make in the preferable treatment for in-patients. Although the authors have so far noted no patient in this study becomes addictive to chlordiazepoxide, but in view of a possible risk of dependence the drug should be used for a limited time on an in-patient basis.

REFERENCES

การใช้ CHLORMETHIAZOLE (HEMINEVRIN) ในอาการจิตอาการขาดสุข

อุตกิกรณ์ ศรีสัณหะ ว.บ.
สมพงษ์ เรืองตรงกูล ว.บ.
เกษมกุล แก้วคุณภักดี ว.บ.

ผู้รายงานได้ทำการทดลองแบบ "double blind" ในคนไข้โรคพิษสุรา 76 ราย ที่ร่วมใช้เป็นคนไข้ของโรงพยาบาลศิริราช เพื่อจะเปรียบเทียบฤทธิ์ของ chlormethiazole (Heminevrin) ซึ่งเป็นยาพ่นขดของยาตามมี 1 Chlorpromazine และ diazepam ในกรณีของกลุ่มอาการขาดสุข มีผลว่าจะมีผลที่ดีเพิ่มขึ้น แต่อาการของอาการขาดสุข ซึ่งอาการนั้น เกรียด ประสงค์หลอก และหวั่นไหว้เหว่า จะปรากฏเหนื่อยในคนไข้ที่ได้รับ chlormethiazole และความร่วมมือในการรักษาของคนไข้ก็มาก

เนื่องจากทุกีในทางป้องกันอาการขาด ระบายประสาท และการทำงานที่เหนื่อยของ chlormethiazole ทำให้หนึ่งแนวคิดว่าควรรักษาคนไข้ที่รับไว้ในโรงพยาบาล ถึงแม้ว่าผู้รายงานจะยังไม่พบการเฉพาะ chlormethiazole แต่ควรออกแบบความเสี่ยงในเรื่องนี้ให้ดี เพราะขณะเดียวควรใช้ยาในเวลาที่ถูกและเหมาะสมกันไข้ในเท่านั้น

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