Biological Correlates of Piracetam Clinical Effects in Psychotic Patients

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The purpose of this controlled clinical trial was to demonstrate possible correlations between changes in bioenergetic metabolism and psychotropic drug administration in the treatment of functional psychosis. The study included twenty-six patients, eleven with schizophrenia, three with chronic atypical depression and twelve with drug-resistant endogenous depressions. All patients were kept on continuous psychotropic medication for at least 3 weeks before starting the trial, and piracetam was given additionally in a fixed dosage of 2400 mg daily; the same number of identical capsules was given during the pre- and post-treatment placebo periods.

Psycho-pathological evaluation of the patients was by the BPRS; clinical and biochemical data were evaluated statistically by the analysis of regression. The results show that in schizophrenic patients an improvement was observed in those cases who had improved biochemically, i.e. where the ATP values had increased. In drug-resistant depressions there was a rapid and significant clinical improvement after piracetam co-administration, and this went in step with a significant rise in ATP levels.

The use of piracetam (which is distributed as Nootropil) is well-known in psychiatric practice. The main indication for this drug is the treatment of organic brain syndromes of different aetiologies (e.g. acute and chronic intoxications, alcoholism included, post-traumatic changes or ageing). Piracetam activates the bioenergetic metabolism of the nerve cells, particularly the synthesis of ATP from ADP, which might be responsible (together with other metabolic consequences) for the restoration of deficient biochemical processes in the CNS. In addition, piracetam was found to interact with the action of some psychotropic drugs at the biochemical level. Rochus and Reuse (1972) described a decrease of $^{32}$p incorporation into phospholipids of the rat brain cortex after chlorpromazine and piracetam counteracted this phenomenon, even if given alone it is almost without such effect. The biological aetiology of schizophrenia and affective disorders could be interpreted as an organic dysfunction of still unknown origin, obviously at subcellular level. We believe that by administering psychotropic drugs to psychotic patients the altered biochemical processes should be normalized if the treatment is successful. However, we still do not know which biochemical processes and in which way.

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In our study we used piracetam as a tool for demonstrating if some correlates could be discovered between the changes in bioenergetic metabolism and the clinical course of functional psychoses during therapy with continuous psychotropic medication and additional treatment with piracetam. The biochemical control of piracetam's action was performed by means of an electrophoretic assessment of ADP and ATP concentrations in the red blood cells of the patients under the experimental therapy. This examination was performed at least twice in each patient, i.e. after the initial placebo period before the active treatment started, and at the end of the additional piracetam therapy before the post-treatment placebo period began. The psycho-pathology was evaluated once a week by an attending physician, the assessment being carried out in a blind fashion. All the patients included in the study were suffering from a functional psychosis, persistent in nature. Patients were kept on constant medication for at least 3 weeks before starting the trial. Nootropil was administered in a fixed dose of 2400 mg per day and the same number of identical capsules was given during both pre- and post-treatment placebo periods.

In the first part of the study fourteen patients entered the trial (ten males and four females; mean age 37 years, range 23–50 years). Schizophrenia was diagnosed in eleven cases, the other three patients suffered from chronic atypical depression. Nine patients were drug-free and were administered only the experimental medication. Five other patients were kept solely on their long-term evening medication (i.e. neuroleptics in a dose corresponding to 25–100 mg of chlorpromazine, or 50 mg of amitriptyline). The active treatment period with piracetam lasted 6 weeks and the psycho-pathology was quantified weekly with the use of the BPRS (Overall & Gorham 1962). The clinical and biochemical data were statistically evaluated using the analysis of regression and compared by the non-parametric method of Spearman’s correlation (Table 1). We found a significantly negative correlation between the BPRS total scores and ATP values both before and after the active treatment period. There was also a significant correlation – a positive one – between the post-treatment values of the BPRS scores and the Q index (i.e. ADP : ATP), while the relationship between the pre-treatment values was not significant. Non-significant relationships were also found between the BPRS scores and ADP values, but the initially negative relationship became positive during the trial. If we differentiate the sample into two sub-groups of seven patients each, i.e. those who improved substantially (by 25% of the initial BPRS scores on average) and those who became worse or improved by less than 5% of the initial psycho-pathology (Figure 1), the following considerations apply:

- the clinical improvement corresponds to an increase of ATP values and vice versa;
- a decrease in ADP values is observed, irrespective of the initial state and psycho-pathological changes during the trial;

Table 1

<table>
<thead>
<tr>
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<th>BPRS:Q</th>
<th>BPRS:ADP</th>
<th>BPRS:ATP</th>
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<tbody>
<tr>
<td>Before treatment</td>
<td>0.175</td>
<td>-0.277</td>
<td>-0.484*</td>
</tr>
<tr>
<td>After treatment</td>
<td>0.729**</td>
<td>0.355</td>
<td>-0.605*</td>
</tr>
<tr>
<td>Percent change</td>
<td>0.604*</td>
<td>0.125</td>
<td>0.618*</td>
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*p < 0.05

**p < 0.01
the Q index increased when the patients' condition deteriorated; a mild decrease was observed in those patients who did not change substantially and a marked decrease was noted in patients who improved very much.

Hypothetically we can presume, that in those patients who are able to react to piracetam therapy by an increase of ATP (even a decrease of ADP and Q index occurred) a clinical improvement might be expected. If there is a decrease of ADP together with ATP values after piracetam therapy, it is more probable that a clinical deterioration or at least no change in the clinical state will occur.

In the second part of our study we examined the clinical and biochemical action of piracetam in another group of twelve patients suffering from drug-resistant depressions (all of them were diagnosed as endogenous depressions; in three cases bipolar, others monopolar). This sample consisted of eleven females and one male, with a mean age of 46 years (range 23–56 years); the average duration of disease was 5 years 6 months (range 2 years 6 months – 14 years) and the present depressive phase had been persisting for 10 months and 2 weeks on average (range 4–30 months). Drug-resistance we defined as a duration of the present depressive phase for more than 3 months and the patients were included into the study when not improved after sufficient doses of tricyclics or

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**Fig 1** Clinical and biochemical effects of Nootropil in psychotic patients. Relative changes during 6 weeks therapy.
Fig. 2. Clinical effects of Nootropil co-administration in drug-resistant depressions (N = 12; HDRS = Hamilton Depression Rating Scale)

Table 2
Nootropil biochemical effects in depressive patients (N = 12): Pre-treatment and post-treatment values (mean ± S D)

<table>
<thead>
<tr>
<th></th>
<th>ADP</th>
<th>ATP</th>
<th>Q</th>
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<tr>
<td>Pre-treatment (Day 0)</td>
<td>13.31 ± 3.60</td>
<td>27.53 ± 6.22</td>
<td>0.496 ± 0.149</td>
</tr>
<tr>
<td>Post-treatment (Day 28)</td>
<td>13.21 ± 3.46</td>
<td>34.16 ± 7.91</td>
<td>0.408 ± 0.157</td>
</tr>
<tr>
<td>t-test</td>
<td>0.069</td>
<td>2.281</td>
<td>1.417</td>
</tr>
<tr>
<td>Significance</td>
<td>NS</td>
<td>p &lt; 0.05</td>
<td>NS (p &lt; 0.25)</td>
</tr>
</tbody>
</table>
MAOI— the same drug dosage was administered for at least 3 or 4 weeks respectively before the inclusion and further throughout the study. The previous therapy was nialamide in the case of six patients (average daily dose 358 mg, range 250–400 mg), in five patients it was imipramine (235 mg, 200–300 mg) and in one patient dibenzepine (720 mg). Piracetam was co-administered during 4 weeks in a dose of 2400 mg per day with both pre- and post-treatment placebo periods. The psychopathology was evaluated by the Global Assessment and quantified by the Hamilton Rating Scale for Depression (Hamilton 1960). In these intractable depressions we observed a surprising improvement during piracetam combined treatment, which started after 3–12 days (mean 5.3 days) according to the Global Assessment. The clinical data were statistically evaluated by the analysis of variance and the Duncan test (see Figure 2). A significant

Fig 3 Individual parameters (clinical rating = HDRS and bio-chemical data) during Nootropil-placebo co-administration in a drug-resistant depressive patient
Fig 4
improvement was found during the trial (at the 0.5% level of probability). The Duncan test revealed a significant difference (at the 1% level of probability) between the rating scores before and after piracetam therapy. The rapid onset of the piracetam effect during the first week was also confirmed by this evaluation. The biochemical data were assessed by the one-tailed t-test (Table 2). The only statistically significant difference was found between the pre-treatment and post-treatment ATP values — there was a marked increase (at the 5% level of probability) during the trial. Because this study of piracetam effectiveness in drug-resistant depressions is still going on, a more complete statistical processing of the data will be considered after completion of the study. However, both the global results obtained up to now and some individual data collected after repeated withdrawal of piracetam (the identical placebo being maintained was followed by relapses of depression (Figures 3 and 4)) — may demonstrate relations between the changes in energy metabolism and the clinical course of the depressive illness.

On the basis of the results presented we may assume that piracetam seems to be an effective treatment at least in some functional psychoses. In the schizophrenic patients we observed an improvement in those cases who improved from the biochemical point of view, i.e. an increase of ATP values occurred. A very surprising and markedly positive effect was found in drug-resistant depressions, viz. a rapid and significant clinical improvement after piracetam co-administration was followed by a significant increase of ATP levels.

Piracetam was shown to be not only a clinically effective agent but also a very useful tool for demonstrating some biochemical backgrounds of the aetiology and pathogenesis of functional psychoses, the energetic metabolism being considered as one of the most important factors. Nevertheless, before drawing final conclusions more detailed biochemical research in a larger number of patients would certainly be desirable.

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