Neuroscience and Behavioral Physiology, Vol. 42, No. 2, February, 2012

On the Use of Cavinton and Cerebrolysin in the Preventive Treatment of Alzheimer's Disease[1]

D. S. Kasatkin

Translated from Zhurnal Nevrologii i Psikhiatrii imeni S. S. Korsakova, Vol. 110, No. 10, pp. 85–86, October, 2010.

The first issue of Zhurnal Nevrologii i Psikhiatrii im. S. S. Korsakova [*S. S. Korsakov Journal of Neurology and Psychiatry*] for 2010 included an article by a group of authors entitled "Potential preventive treatment of Alzheimer's disease: results of a three-year prospective open comparative study of the efficacy and safety of courses of cerebrolysin and Cavinton in elderly patients with mild cognitive deficit syndrome," addressing a comparison of the efficacies of these agents in moderate cognitive dysfunction.

Cerebrolysin is a nootropic agent. It is registered in the Russian Federation for the treatment of Alzheimer's disease, dementia syndromes of various etiologies, and chronic cerebrovascular failure.[2] Cavinton is a member of the pharmacological group of cerebral circulatory correctors and was registered in the Russian Federation for the treatment of acute and chronic cerebral circulatory failure (transient ischemia, progressive stroke, post-stroke states, vascular dementia, cerebrovascular atherosclerosis, post-traumatic and hypertensive encephalopathies, vertebrobasilar failure), as well as for the treatment of mental and neurological disorders (memory impairment, vertigo, headache, aphasia, apraxia, motor disorders) in patients with cerebrovascular failure.[2]

The study inclusion criteria listed by the authors point directly to the search, using specific clinical psychological methods, for the moderate cognitive deficit symptoms typical of Alzheimer's disease. In combination with low points scores on the Khachinski scale and the exclusion of patients with stroke and multi-infarct dementia from the cohort, this points to selection of patients with a high risk of developing Alzheimer's disease without concomitant vascular problems. However, current data indicate that Cavinton cannot be used in the treatment of cognitive impairments of purely neurodegenerative nature. Thus, the choice of reference agent in this study seems somewhat strange. Cerebrolysin was used parenterally at the maximum recommended daily dose (30 ml) and the maximum duration of treatment recommended by the manufacturer (20 days). Cavinton was used orally and at half the maximum dose (15 mg; the maximum recommended by the manufacturer is 30 mg). This type of difference in the routes of administration and dose used casts doubt on the comparability of the results obtained.

The text then states that there were two groups of 55 subjects, comparable in terms of gender and age and having similar points scores on specific tests, though the "Results" section refers to 46 and 42 patients completing three-year treatment courses. Detailed data on the reasons why some of the patients were lost are not given, with the exception of a comment that the reasons were non-medical. Furthermore, the cohorts are again not comparable in terms of the absence of pre-treatment differences. In addition, despite the clear non-normality of the distributions of parameters in the cohorts, the table of baseline data presents means and standard deviations rather than medians, modes, and interquartile ranges, which does not provide sufficient assessment of the comparability of the cohorts. Considering the fact that the Wilcoxon *t* test was used for comparisons, rather than analysis of survival, it is difficult to evaluate the differences seen between the cohorts at three years of treatment using the data presented. Use of the Wilcoxon *t* test for

Yaroslavl State Medical Academy, Russian Ministry of Health.

[1] Ed. note: c.f. S. J. Gavrilova et al., *Neuroscience and Behavioral Physiology*, **41**, No. 4, 391–398 (2011).

[2] Data from www.rlsnet.ru.

0097-0549/12/4202-0121

TABLE 1. Comparison of the Costs of Treatment for the Prevention of Alzheimer's Disease.

Parameter	Cavinton 5 mg No. 50	Cerebrolysin 10 ml No. 5	Exelon 3 mg No. 28
Total number of treatment days in 3 years	28 days; 2 courses; 3 years = 168 days	20 days; 2 courses; 3 years = 120 days	365 days; 3 years = 1095 days
Daily dose	15 mg (3 tablets)	30 ml (3 ampules)	3 mg (1 tablet)
Total dose (tablets/ampules)	168 days (3 tablets/day) = 504 tablets	120 days (3 ampules/day) = = 360 ampules	1095 days (1 tablet/day) = = 1095 tablets
Cost per tablet/ampule	170 rubles (1 pack of 50 tablets) = = 3.4 rubles	1300 rubles (pack of 5 ampules) = = 260 rubles	2278.58 rubles (pack of 28 tablets) = = 81.38 rubles
Total cost of treatment course	504 tablets = 1713.16 rubles	360 ampules = 93,600.00 rubles	1095 tablets = 89,108.75 rubles

pairwise comparison of the groups without the appropriate corrections also seems dubious, given that in both cases differences between four cohorts (before treatment, at 1 year, at 2 years, at 3 years) were compared, which also applies to comparisons of the two groups, as the tests were used to compare values measured in two sets of conditions on the same cohorts of subjects [2].

We will attempt to analyze the data obtained in this study. Analysis of the results of three-year treatment courses gave mean MMSE scores in groups 1 and 2 of 28.6 and 27.9 points, respectively. Data from the guidelines for the use of this scale [3] indicate that scores of 25 and above are regarded as normal, i.e., at three years neither cohort has reached mild dementia (21–24 points) and the 0.7-point difference between the mean values does not have discriminatory clinical significance.

The text of the article notes that "the frequency of diagnoses of Alzheimer's disease during the three years from the start of the study in the group treated with cerebrolysin was 3.5 times lower than that in the group of patients treated with Cavinton." This conclusion is based on the fact that diagnoses of Alzheimer's disease were made in two patients of group 1 and seven of group 2. Using Fisher's angular transformation method, we will compare the results for differences in this measure in the cohorts: two of 46 in group 1 (4.3%) and seven of 42 in group 2 (16.7%), φ^*_{emp} = = 1.987. The empirical value of φ^* is in the zone of uncertainty, i.e., the probability of error was 3% (p = 0.03), though the volume of baseline data and the not entirely correct formation of the initial cohorts, as noted above, prevent any unambiguous conclusion from being drawn in relation to the effects of the agents in terms of preventing the progression of moderate cognitive deficits in Alzheimer's disease. Similarly, comparison of the cohorts in terms of the apoE(+) genotype using Fisher's angular transformation [1] yields a similar result: two out of 26 (7.7%) in group 1 and five of 25 (20%) in group 2, φ^*_{emp} = 1.303, which is in the insignificant zone ($p > 0.05$). Comparison of the cohorts for the apoE(–) genotype by this method is impossible because of the invalidity of the test [1] when the proportion in one cohort is zero: none out of 26 and two out of 25 respectively. The fact of different influences of the different agents on the prevention of Alzheimer's disease depending on their genotypes is very important in terms of early prescription of differential treatment of illness, though the conclusions drawn from this study are somewhat premature.

In this regard, the approximate direct costs of preventing Alzheimer's disease with the agents used in the study as compared with treatment with an agent registered for the treatment of Alzheimer's disease (Exelon) is also significant. We will make calculations of the mean costs using data from an online pharmacy on 06.19.2010: Cavinton 5 mg No. 50 = 170 rubles, cerebrolysin 10 ml No. 5 = 1300 rubles, rivastigmine (Exelon 3 mg) No. 28 = 2278.58 rubles (see Table 1). These calculations show that the cost of treatment with Cavinton is 1713.16 rubles, compared with 93,600 rubles for Cerebrolysin, without any consideration of the costs associated with daytime or overnight hospitalization of the patient. The costs of preventing Alzheimer's disease with cerebrolysin in this study are essentially equivalent to the treatment of moderate dementia with acetylcholinesterase inhibitors for three years (Exelon 3 mg/day = = 89,108.75 rubles).

Comparative studies of the head-to-head type are undoubtedly appropriate for identifying the boundaries for the use of agents and for differentiating their use depending on the clinical characteristics of moderate cognitive disorder, though significant data require multicenter, randomized, double-blind trials with appropriate statistical analyses and independent evaluation of statistical data to exclude incorrect interpretation of the results obtained.

REFERENCES

1. E. V. Sidorenko, *Methods in Mathematical Analysis in Psychology* [in Russian], Rech, St. Petersburg (2003).
2. M. Hollander and D. A. Wolfe, *Nonparametric Statistical Methods* [Russian translation], Finansy i Statistika, Moscow (1983).
3. D. Mungas, "In-office mental status testing: a practical guide," *Geriatrics*, **46**, No. 7, 54–56 (1991).