Oral Citicoline in Acute Ischemic Stroke
An Individual Patient Data Pooling Analysis of Clinical Trials

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Background and Purpose—No single neuroprotective agent has been shown to influence outcome after acute stroke. Citicoline has been studied worldwide in many clinical trials with positive findings, but only 1 trial has obtained significant results in the primary efficacy variables. Our objective was to evaluate the effects of oral citicoline in patients with acute ischemic stroke by a data pooling analysis of clinical trials. The primary efficacy end point chosen was the common evaluation of recovery, combining National Institutes of Health Stroke Scale ≤1, modified Rankin Scale score ≤1, and Barthel Index ≥95 at 3 months using the generalized estimating equations analysis.

Methods—A systematic search of all prospective, randomized, placebo-controlled, double-blind clinical trials with oral citicoline (MEDLINE, Cochrane, and Ferrer Group bibliographic databases) was undertaken. Individual patient data were extracted from each study and pooled in a single data file. The main inclusion criteria included compatible neuroimaging with ischemic stroke, National Institutes of Health Stroke Scale ≥8, and prior modified Rankin Scale score ≤1. Four clinical trials using various doses of oral citicoline (500, 1000, and 2000 mg) were identified.

Results—Of 1652 randomized patients, 1372 fulfilled the inclusion criteria (583 received placebo, 789 received citicoline). Recovery at 3 months was 25.2% in citicoline-treated patients and 20.2% in placebo-treated patients (odds ratio [OR], 1.33; 95% CI, 1.10 to 1.62; $P=0.0034$). The dose showing the largest difference with placebo was 2000 mg, with 27.9% of patients achieving recovery (OR, 1.38; 95% CI, 1.10 to 1.72; $P=0.0043$). The overall safety of citicoline was similar to placebo.

Conclusions—Treatment with oral citicoline within the first 24 hours after onset in patients with moderate to severe stroke increases the probability of complete recovery at 3 months. **(*Stroke*. 2002;33:2850-2857.)**

Key Words: cytidine diphosphate choline ■ neuroprotection ■ stroke, acute ■ stroke, ischemic

Acute stroke is a leading cause of morbidity and mortality worldwide. Although stroke imposes an enormous economic burden, treatment is far from satisfactory. Almost 5 years after the licensing of recombinant tissue plasminogen activator in the United States for selected patients within the first 3 hours of stroke onset, no new drug has been shown to influence outcome after stroke. Within the last few years, a huge number of compounds that interfere with the biochemical mechanisms that mediate ischemic brain injury have been demonstrated to be neuroprotective in preclinical models of stroke. However, all those drugs that survived safety trials and were studied in phase III clinical trials have so far failed to prove efficacy.[1]

Citicoline (or CDP-choline), a compound normally present in all cells in the body, is both a neuroprotective drug, when administered exogenously, and an intermediate in membrane phosphatide biosynthesis. After oral administration, the bioavailability is ≈100%.[2] Citicoline has shown different pharmacological actions, with beneficial effects in some models of cerebral ischemia and synergistic effects with other drugs tested in the treatment of brain ischemia.[2]

Citicoline has been extensively studied in >11 000 volunteers and patients with various neurological conditions.[2] The first well-designed clinical trials in acute stroke patients showed positive results, but the sample size of these studies was small.[3–5] In the 1990s, the clinical development of citicoline for the treatment of acute ischemic stroke was initiated in the United States.[6–10] The first US phase II to III trial[6] was conducted to evaluate the effect of 3 doses (500, 1000, and 2000 mg/d) of citicoline versus placebo. Citicoline

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treatment at 500 and 2000 mg/d demonstrated significant improvement of neurological (National Institutes of Health Stroke Scale [NIHSS]), functional (Barthel Index [BI]), and global (modified Rankin Scale [mRS]) outcomes compared with placebo 12 weeks after stroke onset. In the second study,[7] treatment with citicoline 500 mg showed significant benefits in a subgroup of patients with moderate to severe strokes (baseline NIHSS ≥8) in terms of functional recovery (BI ≥95) compared with placebo. The last trial[9] was designed to confirm the effect of citicoline 2000 mg/d on neurological and functional outcomes of patients with moderate to severe acute ischemic stroke. This study did not demonstrate significant differences in the primary end point (≥7-point improvement in NIHSS score). However, posthoc analyses indicated the potential benefit of citicoline in clinical assessments such as mRS. In radiological assessments, it was shown that citicoline was able to induce a reduction in infarct volume in some patients.[8,10] In all these studies, the overall safety of citicoline was similar to that of placebo.

The National Institute of Neurological Disorders and Stroke (NINDS) held a workshop on statistical approaches to analyzing acute stroke trials that have multiple prespecified outcomes. They concluded that a global statistic estimation of the different outcomes such as NIHSS, BI, Glasgow Outcome Score, and/or mRS should be used to test the primary hypothesis of the trial, accompanied by an analysis of the individual outcomes used in the global test.[11]

In view of the variety of outcomes and inconclusive results but with the same trend in different trials, we decided to perform a meta-analysis of individual patient data to test whether treatment with oral citicoline for 6 weeks improves overall recovery at 3 months for patients with acute ischemic stroke. The primary end point was a global test for multiple outcomes because it allows an overall dimension of recovery for a stroke patient.[11]

Subjects and Methods

The Citicoline Steering Committee was constituted specifically for this study. This committee defined the objectives, methodology, and protocol following the guidelines to perform meta-analyses with updated individual patient data[12] and the statistical guidelines[13] The independent Ethical Committee of the Hospital Universitari Doctor Josep Trueta of Girona (Spain) approved the protocol. A common core of data was extracted from each study and pooled in a single data file. An external Clinical Research Organization (Biométrica SL, Barcelona, Spain) was responsible for checking the data, running the analysis, maintaining confidentiality, and security the data files. A copy of the common file was available for all members of the Steering Committee. The Department of Statistics and Operation Research from Universitat Politècnica de Catalunya audited the final report.

Clinical Trial Selection

A systematic search, following the Cochrane Library Guidelines,[12] was done to identify all prospective trials performed with oral citicoline in stroke. Eligible trials were searched through the MEDLINE Database, Cochrane Database, and Ferrer Group bibliographic database. The primary source of the trials was contacted to achieve further information on each identified trial. To be considered eligible for the data pooling analysis (DPA), clinical trials had to meet the following requirements: (1) placebo-controlled, double-blind, randomized clinical trials with an accurate randomization process carried out with oral citicoline in acute stroke; (2) trials with >10 patients in every group; (3) a treatment period of 6 weeks; (4) identical end points obtained at 3 months with mRS, BI, and NIHSS; and (5) use of good clinical practices.

Criteria for selection of clinical trials were checked manually. A single reviewer discarded irrelevant citations on the basis of the title of the publication and its abstract. If there was any suggestion that the article could possibly be relevant, it was retrieved for further assessment. Two reviewers independently selected trials for inclusion in the review from the citation list. Disagreements were resolved by discussion, and no persisting differences remained. After the exhaustive search, 89 references were found, but only 4 fulfilled the established criteria. The 4 selected trials included in this study were performed in the United States,[6–9] had a total sample of 1652 patients, and used various doses of oral citicoline (500, 1000, and 2000 mg) and placebo.

Patient Selection

The Steering Committee compared protocols and case report forms of eligible trials to identify differences and sources of heterogeneity. A common core of individual patient data was extracted from each study file and pooled in a common data file. Data were checked for accuracy, consistency, and completeness of the follow-up. Tabulated data were sent to each trial representative for verification. All differences were verified, and the data file was updated.

The inclusion criteria for the DPA were as follows: (1) male or female, ≥18 years old; (2) patients randomized within 24 hours after stroke onset; (3) patients with a measurable focal neurological deficit lasting for a minimum of 60 minutes (this deficit must persist from onset and up to the time of treatment without clinically meaningful fluctuation); (4) patients must have a neuroimage compatible with the clinical diagnosis of acute ischemic stroke before randomization; (5) patients must have an acute ischemic stroke with symptoms on clinical examination, suggestive of a stroke referable to the middle cerebral artery territory; (6) baseline NIHSS≥8, with at least 2 of these points from Sections 5 and 6; and (7) mRS ≤1 immediately (ie, minutes) before stroke.

There were 6 exclusion criteria: (1) neuroimage showing brain tumor, cerebral edema with a clinically significant mass midline shift with compression of the ventricles, brainstem or cerebellar infarction, subarachnoid hemorrhage, and intracerebral and/or intraventricular hemorrhage; (2) severe coexisting or terminal systemic disease that limited life expectancy or interfered with the conduct of the study; (3) history of ventricular dysrhythmias, acute myocardial infarction within 72 hours of enrollment, unstable angina, uncompensated congestive heart failure, or any other acute, severe, uncontrollable or sustained cardiovascular condition that, in the investigators' opinion, interfered with effective participation in the study; (4) previous disorder that made interpretation of the neurological scales difficult; (5) psychoactive substance–related disorder or preexisting dementia; and (6) preexisting medical condition (ie, significant renal or hepatic disease) that, in the investigators' opinion, interfered with the patient's suitability and participation in the study.

Efficacy and Safety Assessments

The primary objective of this study was to determine the effect of oral citicoline on recovery after 3 months in patients with moderate to severe acute ischemic strokes (baseline NIHSS ≥8) compared with placebo. The primary efficacy hypothesis was assessed with a global estimation of the effect (odds ratio [OR]) on NIHSS, BI, and mRS using the generalized estimating equations (GEE) method as recommended by NINDS for stroke trials.[11] Assuming that any single outcome measure gives partial information on clinical recovery from stroke, the GEE has been designed to give an integrated and more informative assessment of treatment efficacy based on the combination of the effect on the 3 main scales. This approach has higher statistical power to detect differences between treatments and generates an OR that gives a measure of how the odds of a favorable outcome on treatment compares with the odds of a favorable outcome on placebo in the population.[11] Success on this index does not require success in all 3 single scales, but the response of the individual scales has to be congruent with a positive score. To help

TABLE 1. Patients Screened and Selected for the Analysis in the Original Clinical Trials Identified

	Treatment				
Study	Placebo	C500	C1000	C2000	Total
Clark et al[6]	65 (47)	62 (37)	66 (40)	66 (43)	259 (167)
Clark et al[7]	127 (70)	267 (186)			394 (256)
Warach et al[8]	48 (37)	52 (41)			100 (78)
Clark et al[9]	446 (429)			453 (442)	899 (871)
Total	686 (583)	381 (264)	66 (40)	519 (485)	1652 (1372)

C500 indicates citicoline 500 mg/d; C1000, citicoline 1000 mg/d; and C2000, citicoline 2000 mg/d. Numbers in parentheses are those selected for analysis.

understand what the effects of the treatment can be, we provide a GEE estimate of the placebo and treatment percentages of positive response common over the 3 outcome scales.

Secondary objectives were the assessment of the efficacy of the drug on the individual scales (NIHSS, BI, and mRS), and on the risk of mortality. The consistency of the results in the selected population was verified in a further posthoc analysis of all patients included in the 4 clinical trials. Safety of citicoline was assessed through adverse event reports from every trial and data provided by ECGs, vital signs, biochemistry, and hematology according to preestablished criteria of potentially clinically significant changes.

Statistical Analysis

General Methods

Statistical analysis was conducted according to the intention-to-treat principle. Intent-to-treat population was defined as patients randomized with at least 1 efficacy evaluation after receiving at least 1 medication tablet who met inclusion criteria for this protocol. If no data were recorded at analysis at week 3, 6, or 12, then data were carried forward from the most recent visit (last observation carried forward). To assess sensitivities, analyses were repeated in the per-protocol population, including all randomized patients who also had the final week 12 evaluation. Baseline characteristics, safety assessments, and mortality were described for the overall trials in the 2 treatment groups.

Assessment of the Primary Objective (Global Recovery)

Statistics (Wald test) were done from a generalized linear model with the logit-link function. Using GEE, the analyses combined into a single parameter the observed effect (OR) at week 12 for the 3 outcome variables: BI $\geq$95, mRS $\leq$1, and NIHSS $\leq$1. These were also analyzed separately using the Cochran Mantel-Haenszel procedure as secondary objectives.

Heterogeneity

Both baseline heterogeneity in efficacy variables and heterogeneity in treatment effect were analyzed across studies, the latter being considered more relevant because of the greater potential effect on the study conclusions.[12,13] To take into account the possible heterogeneity of treatment efficacy among studies, interactions between study and treatment effect were included in all efficacy analysis and tested for signification with the χ^2 Wald test. Homogeneity of effect among efficacy variables was inspected by comparing CIs for the effect on any efficacy variable. Statistical heterogeneity in baseline efficacy variables between trials and dose was tested with the Kruskal-Wallis standard test.

Adjustment of the Analysis

In addition to the interaction terms mentioned above, main effects for the baseline characteristics of patients were included in the logistic regression to adjust the effect of different factors that could be confounders with the treatment efficacy. Analysis was performed for patients grouped by stroke severity, time from onset of stroke, risk factors for stroke, and concomitant drugs administered. We included in this analysis only the data that were significantly different between placebo and the different citicoline dose groups.

Statistical Programming and Assumptions

Computations were performed with SPSS version 10.0. The SAS macro GEE version 2.03 was used for the global test of binary outcomes. The probability values presented in this work were 2-tailed.

Results

Patient Characteristics

Of the 1652 patients included in the selected clinical trials, 280 did not fulfill inclusion criteria. The main causes for exclusion were mild stroke (187 patients), therapeutic window >24 hours (80 patients), and mRS before stroke >1 (52 patients). Of the 1372 patients who were evaluated, 789 were randomized to citicoline and 583 to placebo (Table 1).

The patient baseline characteristics are shown in Table 2. Both groups of patients were comparable with respect to demographic data, time from stroke onset to treatment, and

TABLE 2. Demographic Data and Baseline Characteristics

	Placebo (n=583)	Citicoline (n=789)			*P*
Age, mean±SD, y	68.26±12.36	68.52±12.57			NS
Sex, n (%)					
Male	301 (51.6)	376 (47.7)			NS
Female	282 (48.4)	413 (52.3)			
Race, n (%)					
White	468 (80.4)	638 (80.9)			NS
Black	87 (14.9)	118 (15.0)			
Asian	7 (1.2)	10 (1.2)			
Hispanic	12 (2.0)	16 (2.0)			
Other	9 (1.5)	7 (0.9)			
Therapeutic window	13.08±6.36	13.02±6.25			NS
Baseline NIHSS					
Mean±SD, n	14.54±5.09	14.50±5.38			
NIHSS ≥18, %	19	22			NS
		C500	C1000	C2000	0.0032
Median	14	14	17	13	

Abbreviations as in Table 1. Note that when analyzing by dose, there was a significant difference in baseline severity between groups, with the worst neurological status baseline appearing in the C1000 group.

TABLE 3. Risk Factors and Concomitant Therapies

	Placebo (n=583), n (%)	C500 (n=246), n (%)	C1000 (n=40), n (%)	C2000 (n=485), n (%)	*P*
Risk factor					
Previous stroke	111 (19.0)	58 (22.0)	2 (5.0)	97 (20.0)	NS
Previous TIA	111 (19.0)	44 (16.7)	6 (15.0)	80 (16.5)	NS
Carotid disease	85 (14.6)	32 (12.1)	1 (2.5)	77 (15.9)	NS
Family history of stroke	129 (22.1)	37 (14.0)	0 (0.0)	106 (21.9)	0.016
Smoking	265 (45.5)	101 (38.3)	10 (25.0)	213 (43.9)	NS
Excessive alcohol	61 (10.5)	30 (11.4)	4 (10.0)	53 (10.9)	NS
Hyperlipidemia	181 (31.0)	63 (23.9)	7 (17.5)	159 (38.8)	0.034
Diabetes	165 (28.3)	62 (23.5)	13 (32.5)	122 (25.2)	NS
Overweight	115 (19.7)	53 (20.1)	2 (5.0)	103 (21.2)	NS
Coagulopathy	9 (1.5)	3 (1.1)	0 (0.0)	9 (1.9)	NS
Hypertension	404 (69.3)	182 (68.9)	32 (80.0)	355 (73.2)	NS
Congestive heart failure	77 (13.2)	45 (17.0)	2 (5.0)	58 (12.0)	NS
Myocardial infarction	109 (18.7)	65 (24.6)	5 (12.5)	111 (22.9)	NS
Peripheral vascular disease	64 (11.0)	19 (7.2)	7 (17.5)	47 (9.7)	NS
Atrial fibrillation	148 (25.4)	72 (27.3)	7 (17.5)	123 (25.4)	NS
Left ventricular hypertrophy	25 (4.3)	13 (4.9)	3 (7.5)	26 (5.4)	NS
Valvular heart disease	38 (6.5)	20 (7.6)	4 (10.0)	50 (10.3)	NS
Concomitant therapies					
Anticholinergics	24 (4.1)	23 (8.7)	2 (5.0)	26 (5.4)	0.024
Calcium channel blockers	145 (24.9)	88 (33.3)	24 (60.0)	118 (24.3)	0.016
Thrombolytics*	44 (7.5)	1 (0.4)	1 (2.5)	61 (12.6)	0.000

Abbreviations as in Table 1, plus TIA indicates transient ischemic attack. Analyses were adjusted by original study and dose. Statistics were made with χ^2 analysis.

*Thrombolytics use was allowed in the last trial only.

NIHSS score. For risk factors, only family history of stroke and hyperlipidemia differ significantly between groups. Among the concomitant therapies, calcium channel blockers, anticholinergics, and thrombolytics showed a different distribution between groups (Table 3). For thrombolytics, different proportions between placebo and citicoline groups resulted because tissue plasminogen activator (tPA) was allowed only in the ECCO 2000 trial,[9] which in turn included patients who received citicoline 2000 mg. In this trial, the frequency of tPA cotreatment was 11% and 13% in the placebo and citicoline groups, respectively (*P*=NS). Both risk factors and concomitant therapies that were unbalanced were included as covariates in the logistic regression models to control the heterogeneity. Also, highly statistically significant differences in NIHSS at baseline were found between studies. Studies 001a[6] and 007[7] included patients with a more severe stroke than studies 010[8] and 018.[9] Therefore, it was reasonable to expect results of different magnitude from study to study. This did not invalidate the analysis because it had been designed to take into account this kind of heterogeneity and test it for significance. In addition, we showed that the favorable results in the different placebo groups were increasing over time, reflecting the progressive improvement of general management for stroke patients.

Study Completion Status

Table 4 summarizes the study completion status of the patients included in this DPA. No differences for reasons of the study discontinuation between groups were found.

Efficacy Analyses

Primary Objective: Global Recovery

Citicoline was associated with a significantly greater recovery at week 12 (OR, 1.33; 95% CI, 1.10 to 1.62; *P*=0.0034; Table 5). Global recovery was achieved by 25.2% of patients treated with citicoline compared with 20.2% of patients who received placebo. The highest favorable response was observed in the 2000 mg group. Citicoline 2000 mg increased the odds of a favorable outcome compared with placebo by 38% (95% CI, 10 to 72). Of the total patients in the clinical trials (n=1652), global recovery was observed in 31.6% of the citicoline group and in 27.7% of the placebo group (OR, 1.22; 95% CI, 1.01 to 1.45; *P*=0.045). We replicated the analysis in the sample of 1246 protocol-defined patients not treated with tPA and obtained similar results (OR, 1.35; 95% CI, 1.10 to 1.65).

Secondary Objectives

The global effect of citicoline and the effect of each citicoline dose on the individual scales are shown in Figures 1 through

TABLE 4. Study Completion Status

Status	Treatment		
	Placebo (n=583), n (%)	Citicoline (n=789), n (%)	Total (n=1372), n (%)
Patients completed	456 (78.2)	602 (76.3)	1058 (77.1)
Patients discontinued	127 (21.8)	187 (23.7)	314 (22.9)
Reasons for discontinuation			
Adverse stent	6 (1.0)	11 (1.4)	17 (1.2)
Patient request	15 (2.6)	21 (2.7)	36 (2.6)
Noncompliance or uncooperativeness	4 (0.7)	12 (1.5)	16 (1.2)
Investigator decision	3 (0.5)	3 (0.4)	6 (0.4)
Loss of follow-up	3 (0.5)	10 (1.3)	13 (0.9)
Death	96 (16.5)	129 (16.3)	225 (16.4)
Other	0 (0.0)	1 (0.1)	1 (0.1)

3. Compared with placebo, citicoline significantly increased the probability to recover activities of daily living (BI) by 29% (95% CI, 3 to 62) and the probability to recover functional capacity (mRS) by 42% (95% CI, 8 to 88). Citicoline also showed a nonsignificant increase in neurological recovery (NIHSS) of 28% (95% CI, −1 to 65). After adjustment for baseline stroke severity, therapeutic window, primary study, risk factors, and concomitant drugs unbalanced between treatments, the results remained unchanged. In the per-protocol analyses, both primary and secondary objectives showed congruent results with those of the intention-to-treat analyses. When the total sample of patients was analyzed, citicoline showed a significant effect in all 3 scales (Figures 1 through 3).

Mortality

Citicoline had no effect on 3-month mortality (18.8% in the citicoline group, 17.8% in the placebo group; Figure 4). The number of deaths was 52 (19.7%) in C500, 13 (32.5%) in C1000, 83 (17.1%) in C2000, and 104 (17.8%) in the placebo groups (log-rank test, $P=0.781$). Comparison of the C1000 group with the 3 other groups showed a significantly higher mortality ($P=0.019$), which is explained by the same reasons mentioned above. Early deaths (within 14 days) occurred in 131 patients without differences between groups. Causes of death were equally distributed between groups.

Safety

The frequency of the overall adverse events was comparable between groups. Significant differences were found in anxiety (citicoline, 13.7%; placebo, 9.9%; $P=0.036$), leg edema (citicoline, 9.7%; placebo, 6.5%; $P=0.032$), depression (citicoline, 22.5%; placebo, 27.4%; $P=0.038$), falling down (citicoline, 12.57%; placebo, 18.7%; $P=0.002$), and urinary incontinence (citicoline, 10.5%; placebo, 14.0%; $P=0.047$).

Discussion

One of the main reasons for failure in many clinical trials has been an inadequate sample size to obtain significant results in the statistical analysis. In other studies, the primary variable

TABLE 5. Intent-to-Treat Set: GEE-Estimated Probabilities of Global Recovery After 12 Weeks of Follow-Up

	Global Recovery at Week 12				
	Citicoline, %	Placebo, %	OR	95% CI	*P*
Citicoline vs placebo (4 trials, 1372 patients)	25.2	20.2	1.33	1.10–1.62	0.0034
Doses					
Citicoline 500 mg vs placebo					
Study 001a[6]	27.7	11.4	2.98	1.25–7.02	0.0129
Study 007[7]	24.2	16.6	1.61	0.93–2.78	0.0890
Study 010[8]	17.1	24.0	0.65	0.28–1.48	0.3078
Overall	20.8	15.7	1.42	0.96–2.093	0.0782
Citicoline 1000 mg vs placebo					
Study 001a[6]	9.1	10.7	0.84	0.35–2.15	0.7096
Citicoline 2000 mg vs placebo					
Study 001a[6]	25.19	9.8	3.098	1.18–8.12	0.0214
Study 018[9]	28.47	23.25	1.314	1.0–1.65	0.0183
Overall	27.9	21.9	1.38	1.10–1.72	0.0043

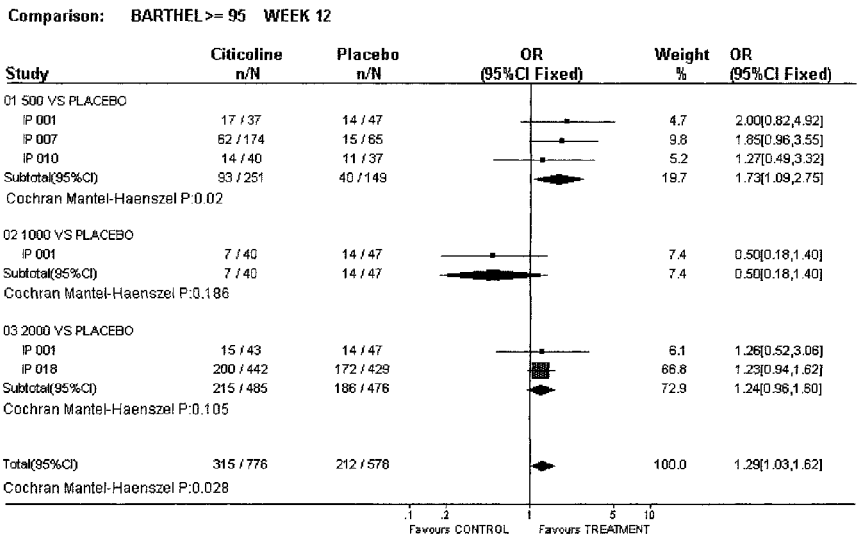

Figure 1. Treatment effect on the recovery of activities of daily living (BI ≥95) 3 months after stroke in the protocol-defined patients. Posthoc analysis for the overall effect on unrestricted population gave an OR=1.22 (95% CI, 1.004 to 1.44). These significant positive results were not replicated when success for BI was defined as ≥60 (OR=1.05; 95% CI, 0.83 to 1.31).

for efficacy was not well chosen to demonstrate the clinical benefits of the drug, while secondary variables showed a beneficial effect.[14] Variation in the magnitude but not in the direction of the treatment effect in citicoline trials probably reflects these drawbacks in clinical trial design.

Meta-analysis, by pooling the individual patients' data from a number of studies, is required to improve the quality of our estimations. An appropriate statistical analysis can, in addition, control for confounding patient characteristics and explore possible sources of heterogeneity between trials.[12,15] In 1996, an NINDS-sponsored committee developed guidelines for the analysis of acute ischemic stroke treatment.[11] Their major contributions were the standardization of patient inclusion criteria and the proposal of a simultaneous, common, or global test for multiple outcomes as the primary end point in stroke trials. Therefore, the aim of this study was to resolve conflicting results in citicoline trials by using a DPA of global recovery in patients who met preestablished selection criteria.

This systematic review is the first to obtain positive results with a potential neuroprotective agent. Prior meta-analyses had failed to demonstrate efficacy of other drugs such as calcium antagonists[16] and tirilazad.[17] In patients with moderate to severe ischemic stroke, oral citicoline for 6 weeks increased by 33% the global odds of recovery at 3 months compared with placebo. This result remained consistent after adjustment for potential confounders of treatment effect, was similar in the intention-to-treat and per-protocol analyses, and was supported by the full recovery observed in individual functional scales, such as BI and mRS. Importantly, citicoline was as safe and well tolerated as placebo and had no effect on mortality. The highest favorable response was observed in the 2000 mg group. The lack of beneficial effect in the citicoline 1000 mg group may be attributed to the small number of patients who received this dose compared with the other doses, combined with a greater stroke severity with a median baseline NIHSS for citicoline 1000 mg of 17.0 compared with 14.0 in the placebo group, 14.0 in the 500 mg group, and 13.0 in the 2000 mg group (P=0.0032, Kruskal-Wallis; Table 2).

The present meta-analysis overcomes many of the limitations of analyses based on summary data extracted from clinical trial reports. Falsely positive results resulting from publication bias may be reasonably excluded because the DPA protocol reviewed the primary sources of information. The selection criteria for the inclusion of trials in this DPA allowed us to avoid the main causes of heterogeneity such as

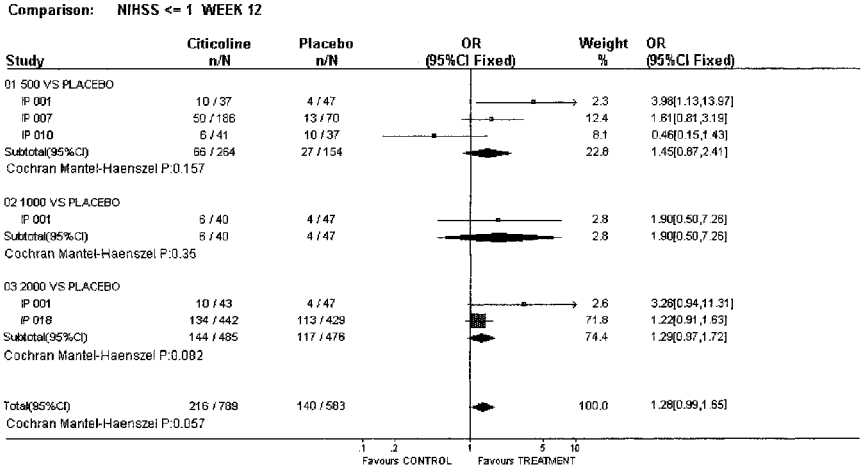

Figure 2. Treatment effect on neurological recovery (NIHSS ≤1) 3 months after stroke in the protocol-defined patients. Posthoc analysis for the overall effect on unrestricted population gave an OR=1.27 (95% CI, 1.004 to 1.60).

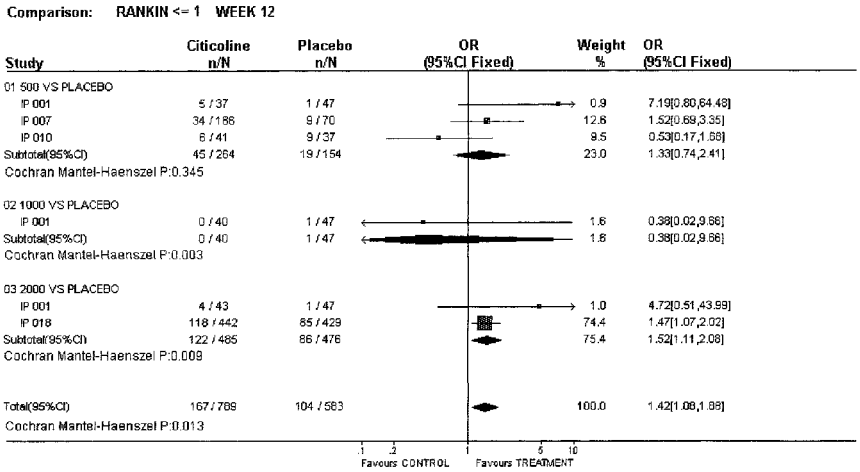

Figure 3. Treatment effect on the functional recovery (mRS ≤1) 3 months after stroke in the protocol-defined patients. Posthoc analysis for the overall effect on unrestricted population gave an OR=1.32 (95% CI, 1.05 to 1.65). These results were similar when success for mRS was defined as ≤2 (OR=1.38; 95% CI, 1.09 to 1.75).

different treatment regimes, therapeutic windows, patient characteristics, diagnostic methods, and variables to evaluate treatment effect. Both groups were adjusted at baseline, particularly in terms of stroke severity, and protocol compliance was high in the citicoline and placebo groups.

A fundamental point of this analysis is that patients with mild strokes were not included in the main analysis. Mild strokes (NIHSS <8) are less prone to benefit from any therapeutic intervention because they have a good prognosis.[18,19] This decision was adopted by the Steering Committee because only patients with moderate to severe strokes were treated in the larger citicoline trial,[9] which was designed after the drug failed in the mild stroke subgroup of a previous study.[7] However, a posthoc analysis of all patients showing a favorable outcome supported the results observed in the selected population. In the same way, the posthoc analysis in the protocol-defined patients not receiving tPA supported the effects of the drug.

Citicoline is the only putative neuroprotectant that has shown partial positive results in all randomized, double-blind individual trials and that has demonstrated efficacy in the predefined primary end point of a meta-analysis. In contrast with many other drugs that have failed in the treatment of stroke within the first 6 hours,[20] citicoline proved efficacy when administered within 24 hours after symptom onset. In addition, citicoline did not cause side effects that have been postulated as contributors to the failure of other agents. So, although the capacity of citicoline to rescue ischemic tissue may be limited, its safety profile likely provides a favorable risk-to-benefit ratio.

In conclusion, treatment with oral citicoline within the first 24 hours after symptom onset in patients with moderate to severe stroke increases the probability of complete recovery at 3 months. A new trial to confirm these results should be conducted.

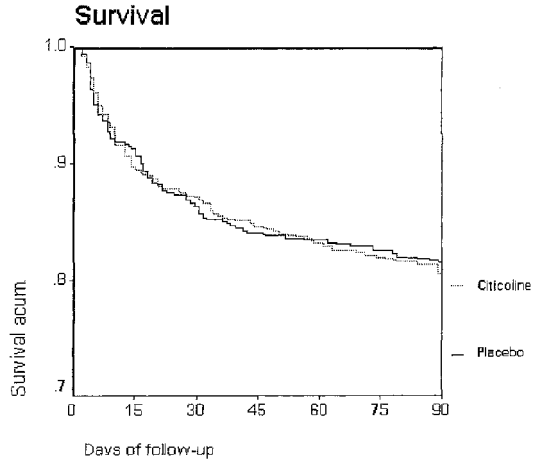

Figure 4. Survival analysis by treatment groups. No differences were found.

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