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Clinical Trial of the Neuroprotectant Clomethiazole in Coronary Artery Bypass Graft Surgery

A Randomized Controlled Trial

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Background: **The neuroprotective property of clomethiazole has been demonstrated in several animal models of global and focal brain ischemia. In this study the authors investigated the effect of clomethiazole on cerebral outcome in patients undergoing coronary artery bypass surgery.**

Methods: **Two hundred forty-five patients scheduled for coronary artery bypass surgery were recruited at two centers and prospectively randomized to clomethiazole edisilate (0.8%), 225 ml (1.8 mg) loading dose followed by a maintenance dose of 100 ml/h (0.8 mg/h) during surgery, or 0.9% NaCl (placebo) in a double-blind trial. Coronary artery grafting was completed during moderate hypothermic (28–32°C) cardiopulmonary bypass. Plasma clomethiazole was measured at several intervals during and up to 24 h after the end of infusion. A battery of eight neuropsychological tests was administered preoperatively and repeated 4–7 weeks after surgery. Analysis of the change in neuropsychological test scores from baseline was used to determine the effect of treatment.**

Results: **Neuropsychological assessments were completed in 219 patients (110 clomethiazole; 109 placebo). The mean plasma concentration of clomethiazole during surgery was 66.2 μM. There was no difference between the clomethiazole and placebo group in the postoperative change in neuropsychological test scores.**

Conclusion: **Clomethiazole did not improve cerebral outcome following coronary artery bypass surgery.**

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THE efficacy of coronary artery bypass surgery in the relief of angina and in some circumstances in enhancing life expectation is now accepted. It is a tribute to the low mortality of the procedure that interest is now focused on the neurologic and neuropsychological complications.[1–3] Adverse neurologic outcomes have been found to occur in 2–6% of patients and neuropsychological deficits in 10–30%.[4–6] These complications are considered to be ischemic in nature, being a consequence of macroembolism and microembolism or impaired cerebral perfusion. Attempts to reduce the frequency or severity of neuropsychological deficits have included modifications to surgical[7] and anesthetic[8,9] management, equipment design,[10] and pharmacologic neuroprotection.[11–13] Some of these interventions have been shown to be effective in demonstrating the sensitivity of neuropsychological testing in this context.[8–10,13]

Clomethiazole enhances γ-aminobutyric acid type A receptor activity and has a long history of use as an anticonvulsant and sedative, particularly in the treatment of ethanol withdrawal.[14] In 1991, Cross *et al.*[15] reported that clomethiazole was neuroprotective in a gerbil model of forebrain ischemia, and further studies have since confirmed that this agent is protective in both focal and global models of cerebral ischemia.[16–19] The first prospective randomized clinical trial of clomethiazole in acute stroke (CLASS)[20] showed some promising results, and another large multicenter study has recently been completed.

Coronary artery bypass surgery offers another opportunity to investigate pharmacological neuroprotection in a clinical context with a quantifiable outcome, but where the timing of drug administration in relation to the cerebral insult can be controlled. In this study we hypothesized that clomethiazole would be neuroprotective in patients undergoing coronary artery bypass grafting (CABG) and that this effect would be verified by an improvement in postoperative neuropsychological performance.

Materials and Methods

Study Design

A prospective, randomized, placebo-controlled, double-blind trial was designed to assess the efficacy of clomethiazole as a neuroprotectant in coronary artery bypass surgery. To recruit an adequate number of pa-

tients within a reasonable study duration, the study was conducted at two cardiac surgical centers: Middlesex Hospital (London, United Kingdom) and Wake Forest University Medical Center (Winston-Salem, NC). Approval for the study was obtained from the ethical review committees at both hospitals. Participants were given written and verbal information about the study before we obtained their written consent. All patients (age $\geq$ 50 yr) listed for standard (not minimally invasive) first-time or repeat coronary artery bypass were considered for the study. Patients were excluded if it was difficult to assess their preoperative neuropsychological status and if they had a need for other concurrent vascular and surgical procedures or emergency surgery on the day of admission, chronic hepatic disease, serum creatinine concentration greater than 200 μM, acute or severe chronic respiratory insufficiency, known intolerance of clomethiazole, known alcohol or drug dependence, or if they were breast feeding or pregnant women or women of child-bearing potential. Patients were also excluded if they received cimetidine within the last 7 days, as this inhibits metabolism of clomethiazole. No patient was rejected because of the clinician's perception of operative mortality or the risk of adverse cardiac or neuropsychological and neurologic outcome. A computer-generated randomization sequence was used to allocate patients to either clomethiazole or placebo and also to balance the two treatment groups within each center. All clinicians, investigators, and patients were blinded to treatment allocation.

Neuropsychological Assessments

The patients' neuropsychological performance and mood were assessed 1 day before (baseline) and 4–7 weeks after surgery, by the same psychologist on both occasions when possible. This postoperative interval was chosen to coincide with a routine clinical visit and is in common use in this context. The eight neuropsychological tests that were administered assess the domains of attention and concentration (Trail Making Test A, Trail Making Test B, Letter Cancellation, Symbol Digit Substitution, and Choice Reaction Time), visuomotor skills (Grooved Pegboard for dominant and nondominant hands), visual memory (Nonverbal Memory), and verbal memory (Rey Auditory Verbal Learning).[21–26] Parallel forms of the tests, where available, were used postoperatively. To determine the influence of mood on cognitive change, the Spielberger State-Trait Anxiety Inventory[27] and the Center for Epidemiologic Studies–Depression[28] scales were used to measure the levels of anxiety and depression, respectively.

Patients were carefully examined for neurologic dysfunction on the day before surgery, daily after surgery until hospital discharge, and at the 4–7 week follow-up. Patients suspected to have developed new postoperative neurologic deficits were seen by a neurologist and, where appropriate, were scored on the National Institutes of Health stroke scale. Serious adverse events were recorded prospectively to the final follow-up assessment.

Anesthesia, Surgery, and Postoperative Management

A standardized anesthesia technique was used that was similar to that used routinely by the cardiac anesthetists at the two centers. Patients were premedicated with intramuscular morphine (7.5–10 mg) and hyoscine (0.2–0.3 mg) or oral diazepam (5 mg). Anesthesia was induced with midazolam (0.1–0.2 mg/kg), fentanyl (10–15 μg/kg) or sufentanil (10–15 μg/kg), and pancuronium (0.1–0.15 mg/kg). After tracheal intubation, the lungs were ventilated with nitrous oxide and oxygen. Anesthesia was maintained throughout the procedure with 0.5–1.5% isoflurane. The cardiopulmonary bypass (CPB) circuit was primed with a crystalloid solution and included a membrane oxygenator and 40-μm arterial line filter. Hypothermic CPB was initiated after heparin (300 IU/kg) was given, and an activated clotting time of greater than 400 s was confirmed. A roller pump maintained nonpulsatile systemic blood flow at 2–2.4 $l \cdot min^{-1} \cdot m^{-2}$, and phenylephrine, isoflurane, or phentolamine was used as required to achieve target mean arterial pressure in the 60–90-mmHg range. The patients were cooled to a nasopharyngeal temperature between 28°C and 32°C during CPB and rewarmed to 37°C before weaning. The technique of myocardial protection was according to the surgeon's usual practice, which was intermittent aortic cross clamp and fibrillation or crystalloid cardioplegia in the United Kingdom, or blood cardioplegia in the United States. At the end of surgery, patients were transferred to the intensive care unit, where mechanical ventilation was continued until the local criteria for weaning and tracheal extubation were met. Sedation was maintained by midazolam infusion, and intravenous morphine was given for analgesia. Within the first 7 days of surgery, drugs investigated for their neuroprotective potential, such as thiopentone, propofol, and nimodipine, were prohibited, as was cimetidine because it inhibits clomethiazole metabolism.

Study Drug Infusion

The study drug was prepared as a colorless solution in clear 500-ml glass bottles. Each bottle contained clomethiazole edisilate (8 mg/ml in 0.8% sodium chloride solution) or 0.9% sodium chloride solution, the placebo. The bottles were stored at 4–8°C but left at room temperature for at least 12 h before use. After induction of anesthesia, a volumetric pump (IVAC 570; Alaris Medical Systems, San Diego, CA) infused the drug *via* a nonsorbing fluid administration set into a peripheral arm vein. This technique was preferred to the use of a central venous catheter to make it possible to start the infusion at the earliest point after induction of anesthesia.

In animal studies, maximal neuroprotective effects were observed at a plasma clomethiazole concentration in the region of 50 μM when the drug was infused for a short duration (2 h).[18,29] We therefore chose this as the target plasma concentration during surgery. This was achieved by infusing a loading dose of 225 ml over 45 min (equivalent to 1,800 mg clomethiazole edisilate) followed by a maintenance infusion of 100 ml/h until the end of surgery (defined as at completion of the last skin suture). The study drug was terminated at this point to avoid postoperative sedation and on the basis that the period of potential cerebral damage had been covered. No adjustment for weight was made because an open-label pilot study demonstrated that weight-based dosing increased variation in blood concentrations relative to giving all patients a single, defined dose.

Plasma Clomethiazole Concentration

Plasma clomethiazole concentration was measured from blood samples drawn immediately before the start of the drug infusion, immediately before switching to the maintenance infusion, and 30 min later. Further samples were taken immediately before completion of the infusion and 30 min, 1 h, 4–10 h, and 24 h after end of infusion. At each time point, 5 ml of central venous blood was collected in heparinized glass tubes, and after centrifugation for 10 min at 3,000 rpm the plasma was transferred by glass pipette to polypropylene tubes and stored at −20°C. Plasma clomethiazole concentration was measured by reversed-phase liquid chromatography and ultraviolet detection at the Department of Bioanalysis, Astra Arcus AB, Sweden. A population pharmacokinetic analysis was performed. The individual average plasma concentration during surgery could be estimated in 123 patients from the final population pharmacokinetic model, posterior Bayesian feedback, and the individual dosing regimen. Average plasma concentration was calculated as area under the curve during surgery divided by duration of surgery.

Cerebral Emboli Monitoring

As a measure of cerebral embolic "load," we monitored and recorded onto videotape the spectral display obtained by Doppler ultrasound of the middle cerebral (United Kingdom center) or the common carotid artery (US center) using a pulsed 2-MHz transcranial device (Pioneer TC4040; Nicolet-EME, Germany) or continuous-wave 5-MHz Doppler (Carolina Medical Electronic, King, NC), respectively. These different techniques were used as they reflected institutional practice and available expertise in the two centers. Embolic signals were identified using previously recommended criteria,[30] and the number of such signals were counted offline, blind to neuropsychological outcome and treatment group.

Statistical Analysis

Conventionally, neuropsychological deficit has been defined as a decrease of more than 20% or one SD in a patient's postoperative test score compared with baseline. The use of a cutoff score in this way can be criticized for lacking sensitivity and failing to take account of improvements in performance.[13,31] Therefore, as the primary analysis in this study, we examined the change in score from baseline, which provides a continuous measure of neuropsychological performance. Secondary analysis, using the conventional cutoff measure of a 20% decline, was performed to allow comparison with other studies.

The differences in neuropsychological change between the active drug and control group can be summarized by performing a global test using the general least squares (GLS), ordinary least squares (OLS), and nonparametric statistics as proposed by O'Brien[32] and Lemacher *et al.*[33] The GLS and OLS statistics are both parametric tests and differ in respect to how the weights for combining the neuropsychological test scores are defined. The weights for the GLS statistic are determined by the correlation between individual test scores, whereas equal weights are assigned to all scores in the OLS test. The GLS test was defined as the primary analysis in the study, and the purpose of conducting the two other tests was to address the robustness of the primary result. To account for any differences between the two centers and between treatment groups for the baseline test scores, the O'Brien test statistics were calculated on the basis of the residuals from analysis of covariance models. Any effects of the differing treatments were retained by adding back in the treatment group least square means estimated in the analysis of covariance model. The O'Brien OLS test is very similar to a global Z score. The intention was to make a global statement of the effects seen across the complete battery of neuropsychological tests. The O'Brien tests have maximum power when all components point in the same direction.

For the secondary analysis, deficit in an individual test was defined as a decrease of more than 20% in that patient's test score from baseline to the week 4–7 postoperative follow-up assessment.[26] In tests assessed by the time to completion, a deficit or a 20% worsening was indicated by a 20% increase in time taken to complete the task. In tests assessed by the number of correct answers, we defined a deficit as a 20% decrease in score from baseline. Subjects were considered to have an overall neuropsychological deficit if they had adverse changes of 20% of more in two or more tests.

Sample size was determined for the primary analysis and based on the GLS-test of O'Brien, which in turn is based on the model:

$$\mu_{1i} - \mu_{2i} = \lambda\sigma_i,\ I = 1,\ 2,\ \ldots\ 10$$

Table 1. Nonfatal Serious Adverse Events

Adverse Event	Clomethiazole	Placebo
Respiratory	6	7
Infection	7	5
Cardiac	4	6
Blood loss	2	1
Stroke	0	2
Hypotension	1	1
Excessive sedation	1	0
Gastrointestinal tract	1	2
Other	0	2

where μ_{ji} is the change from baseline to follow-up in the *i*th neuropsychological test in treatment group j, and σ_i is the common SD in each treatment arm. The null hypothesis is $\lambda = 0$, and the one-sided alternative is $\lambda > 0$. It was determined that a sample size of 110 patients per treatment group would be required for detecting a difference between the treatment groups based on the following assumptions: (1) an overall nominal one-sided significance level of 2.5%; (2) a power of 90%; (3) a minimum detectable difference between treatment groups of $\lambda = 0.25$; and (4) correlations between the outcomes on the various neuropsychological tests were of the same size and equal to 0.25. This corresponds approximately to an effect-size of 0.5 words for the Rey Auditory Verbal Learning Test and 4 s for Trailmaking Test A. Assumptions (3) and (4) were based on data on file.

Results

Study Populations

Between May 1997 and November 1998, 124 patients were randomized to receive clomethiazole and 121 to placebo. One patient was withdrawn from the study before arrival in the operating room by the anesthesiologist in charge of the case; this patient was retained in the randomized (placebo) group as the treatment number had already been assigned. Two patients, both in the clomethiazole group, were withdrawn from the study before the drug infusion was completed: one patient, who died during surgery, failed to wean from CPB because of severe myocardial ischemia from a failed anastomosis; the other suffered a suspected anaphylactoid reaction to protamine and died of intractable cardiac failure 3 days postoperatively. Five clomethiazole and two placebo patients died before the 4–7-week follow-up assessment, with the time of death ranging from the day of surgery to 28 days after surgery. There was no obvious relation to treatment with clomethiazole and no significant difference between the treatment groups for total deaths (7 clomethiazole, 2 placebo). Serious adverse events were reported in a further 22 patients (18%) in the clomethiazole-treated group and in 26 patient (21%) in the control group (table 1).

Six patients (4 clomethiazole, 2 placebo) did not complete the full test battery at one or both assessments, and 10 patients did not attend the hospital for follow-up assessment 4–7 weeks after surgery (3 clomethiazole, 7 placebo). Two (one in each group) refused, two (one in each group) withdrew because of adverse events, and six (one clomethiazole, five placebo) were lost to follow-up. Therefore, of the 244 patients who received the study drug, 25 (10.2%) were excluded from the efficacy analysis (14 clomethiazole, 11 placebo).

Table 2. Demographic Characteristics for Clomethiazole and Placebo Groups

Characteristic	Clomethiazole (n = 124)	Placebo (n = 121)
Age (yr)	64.6 ± 7.4	64.5 ± 7.5
Male:female (n)	110:13	91:29*
Height (cm)	172.8 ± 8.3	171.4 ± 7.9
Weight (kg)	84.1 ± 13.7	80.1 ± 12.7

Data are mean ± SD.

* Chi-square = 7.82; $P < 0.01$.

Patient Characteristics

The demographic characteristics of the two groups were similar with respect to age, height, and weight, but there was a larger ratio of male to female patients in the clomethiazole group (table 2). The duration of CPB and surgery, the number of grafts, and the number of emboli were similar in the two groups (table 3). Temperature was the same in both groups (clomethiazole: mean = 34.6°C, range = 30–36°C; placebo: mean = 34.8°C, range = 33–37°C). The time to extubation, however, was significantly longer in the clomethiazole group (table 3). As shown in table 4, the two groups did not differ in their baseline neuropsychological test scores or the measures of anxiety and depression.

Dose and Plasma Clomethiazole Concentration

The total dose given to patients was dependent on the duration of surgery. The mean dose administered was 54.5 mg/kg (SD 12.5), and the average plasma clomethiazole concentration during surgery was 66.2 μM (coefficient of variation, 13.4%). Despite the use of a peripheral

Table 3. Surgical Characteristics for Clomethiazole and Placebo Groups

Characteristic	Clomethiazole (n = 124)	Placebo (n = 120)
Duration of CPB (h)	1.5 ± 0.59	1.5 ± 0.61
Duration of surgery (h)	3.7 ± 1.04	3.6 ± 0.89
Number of grafts	3.29 ± 0.83	3.19 ± 0.8
Number of emboli	378 ± 639	387 ± 646
Time to extubation (h)	28.6 ± 67.7	15.6 ± 50.7*
Median (h)	16	12.3

Data are mean ± SD.

CPB = cardiopulmonary bypass.

* $P < 0.01$.

Table 4. Neuropsychological Test Scores and Mood Assessments by Treatment Group before Surgery and at Weeks 4–7

	Clomethiazole (n = 110)		Placebo (n = 109)	
Neuropsychological Test	Preoperative	4–7 wk	Preoperative	4–7 wk
Trailmaking test A (s)*	44.7 ± 16.4	39.6 ± 13.5	45.6 ± 16.0	41.8 ± 17.0
Trailmaking test B (s)*	101.6 ± 43.1	91.0 ± 39.9	108.1 ± 47.9	100.6 ± 60.8
Letter cancellation (s)*	112.9 ± 33.1	111.7 ± 29.3	115.1 ± 31.8	113.1 ± 33.7
Grooved pegboard, dominant (s)*	85.4 ± 20.9	81.2 ± 20.1	87.2 ± 28.6	82.4 ± 23.5
Grooved pegboard, nondominant (s)*	93.5 ± 28.0	88.9 ± 25.0	93.8 ± 24.4	89.7 ± 20.4
Symbol digit substitution (s)*	202.1 ± 51.9	187.2 ± 50.2	208.1 ± 59.6	195.1 ± 58.0
Nonverbal memory†	17.2 ± 2.2	17.8 ± 1.7	17.4 ± 1.7	17.8 ± 1.8
Rey Auditory Verbal Learning Test‡	50.4 ± 12.4	54.4 ± 14.3	53.0 ± 13.5	54.8 ± 14.6
Choice reaction time (ms)§	657.8 ± 209.6	663.3 ± 199.5	676.8 ± 237.5	636.2 ± 172.7
STAI‖	34.1 ± 9.7	28.6 ± 8.2	35.9 ± 11.1	29.9 ± 9.9
Depression (CESD)‖	10.6 ± 8.4	9.3 ± 8.0	12.0 ± 9.7	9.7 ± 8.8

Data are mean ± SD.

* Time to completion. † Number of items correct (maximum 20). ‡ Total number of words recalled in seven trials (maximum 105). § Mean response time. ‖ Score on questionnaire (see references 27 and 28).

STAI = Spielberger State-Trait Anxiety Inventory; CESD = Centre for Epidemiologic Studies—Depression Scale.

vein for the drug infusion, there was no excess of phlebitis in those given the active agent.

Neuropsychological Outcome

The results of the nonparametric tests before and after surgery for the treated and placebo groups are shown in table 4. There was a tendency for improved performance on the second assessment for both groups in all tests with the exception of the clomethiazole group in the Choice Reaction Time task, where performance was slower postoperatively. There was no evidence of any difference in the effect of the drug between the two centers. There were too few women for reliable separate analysis of any sex difference in drug effect.

The primary endpoint, the global test statistic calculated by the GLS, OLS, or nonparametric methods, did not indicate a statistically significant difference between the two groups (table 5). When postoperative neuropsychological deficit was defined as a postoperative decline of 20% or more of the individual's baseline score in two or more tests, there was no difference between the two groups. Both groups showed lower-than-predicted deficits on this secondary outcome. When an analysis was made of the postoperative change on each test using the change score (Z),[13] although the majority of tests showed a trend toward a better outcome for patients in the clomethiazole group, this difference was also not statistically significant. In summary, none of the methods of analysis demonstrated a significant difference between patients randomized to clomethiazole or placebo. Anxiety or depression did not influence the neuropsychological changes and were not different between the groups. Of three patients who developed postoperative stroke, one received clomethiazole and two received placebo.

Table 5. General Least Squares, Ordinary Least Squares, and Nonparametric Global Test of Treatment Effect

	Treatment Effect	
Method of Calculation	*t* Statistic	*P* Value
GLS	0.610	0.271
OLS	0.435	0.332
Nonparametric	0.278	0.390

GLS = general least squares; OLS = ordinary least squares.

Discussion

This study is the first to evaluate the use of clomethiazole in cardiac surgery. The plasma concentration achieved was similar to that shown to be neuroprotective in animals. However, we did not find a difference in neuropsychological outcome between patients who received clomethiazole or placebo during coronary artery bypass surgery.

Neuropsychological assessment has proved to be a sensitive measure for evaluating a range of interventions in cardiac surgery, including choice of oxygenator, *p*H management strategy, and use of filters.[31] We used a continuous measure of neuropsychological performance that takes into account postoperative improvement as well as deterioration. This approach increases the information obtained from the battery of neuropsychological tests and, we believe, better represents the impact of the intervention on overall neuropsychological performance. Conventionally, however, neuropsychological assessment has relied on a dichotomous definition of postoperative deficit according to arbitrary degrees of deterioration in test score.[31] Both analyses were used in this study, and neither demonstrated a significant effect of clomethiazole on neuropsychological outcome. However, the deterioration seen in the placebo group was less than anticipated at the planning stage. This may have been a result of the rigorous exclusion criteria. As a result, the study may have been underpowered.

Clomethiazole is neuroprotective in experimental models of cerebral ischemia, and we hypothesized that this effect could be translated to a reduction in the deleterious effect of cardiac surgery on neuropsychological performance. Whereas these models are considered to be representative of stroke or global cerebral hypoperfusion (as may occur in cardiac arrest, for example), they may not mirror either the severity or mechanism of cerebral injury associated with cognitive dysfunction after cardiac surgery. Clinical and neuropathologic evidence suggest that cerebral microemboli, which can be detected principally during CPB, may lead to multiple foci of ischemic damage.[34] However, not enough is known about the critical number and physical characteristics of these emboli, their size, the severity of neuronal injury they produce, or their final anatomic location and correlation with neuropsychological outcome. We obtained a measure of the embolic load using Doppler ultrasound monitoring of the middle cerebral or carotid arteries and found no difference between the groups. But as we could not be more precise about the characteristics of the emboli, which is likely to determine their propensity to induce ischemic lesions, we cannot be certain that the degree of cerebral injury was necessarily similar in the two groups.

A large multicenter, randomized, double-blind, controlled trial of clomethiazole in major acute stroke has just been completed, and the preliminary results (presented by Patrick D. Lyden, M.D., University of California, San Diego, at the International Stroke Conference in Melbourne, Australia, November 26–29, 2000) suggest that clomethiazole did not improve outcome compared with placebo. Despite the evidence from animal models for a role for γ-aminobutyric acid in the pathophysiology of ischemia and for neuroprotection from agents such as clomethiazole[15] and muscimol,[35] so far it appears that there are no such parallels in humans.

In our study, the drug caused longer extubation times, which can probably be attributed to its sedative properties, although serious adverse events were no more common in the treated group (28 *vs.* 29). There were, however, more deaths in the treated group, but this difference was not significant, and the clinical data did not suggest that these were drug-related.

In conclusion, clomethiazole could be safely given to patients undergoing CABG, but an infusion regimen achieving plasma concentrations commensurate with neuroprotection in animal models failed to show any such effect in this trial. Improved practice is apparently leading to reduced neuropsychological adverse outcome following this common surgery but is still sufficiently frequent to justify continued attempts at cerebral protection. However, the evidence for the efficacy of pharmacologic neuroprotection during cardiac surgery is scanty. Drugs of demonstrated efficacy in animal models have not yet shown any clinical value in CABG and little neuroprotection in stroke.

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