CONTROLLED TRIAL OF ORNITHINE ALPHA KETOGLUTARATE (OAKG) IN PATIENTS WITH STROKE

M. L. WOOLLARD, R. M. PEARSON, G. DORF, D. GRIFFITH, AND I. M. JAMES

SUMMARY A double blind controlled trial of ornithine alpha-keto glutarate (OAKG) was carried out on 50 patients admitted to the Royal Free and Royal Northern Hospitals, London, suffering from a recent stroke. Significant improvement was found in patients treated with OAKG when examined on the fifth day of therapy as compared to their control cases. The therapy was given for 5 days. When the patients in the treated and the control groups were compared 10 days after the beginning of treatment, there were no differences between the 2 groups. Implications of these findings are discussed.

THE DRUG ornithine alpha ketoglutarate (OAKG) has been used for many years in Europe for the treatment of hepatic encephalopathy. It has been shown to reduce blood ammonia concentration and to partly reverse the brain metabolic changes of hepatic encephalopathy but in clinical use for fulminant hepatitis it has been less successful.

Both experimental hypoxia and ammonia intoxication in animals have long been known to provoke cerebral anaerobic glycolysis with resultant lactate formation. The anaerobic glycolysis due to hyperammonemia can be attenuated by the administration of ornithine alpha ketoglutarate. The mechanism by which these changes occur has not been established. Possible mechanisms include the bypassing of the pyruvate decarboxylase stage of glucose breakdown or the replenishing of the intermediates of the citric acid cycle depleted by ammonia. For many years glucose was considered to be the only substrate that the brain could use. This is now known to be incorrect. Since brain glucose consumption falls and oxygen rises after or-
nithine alpha ketoglutarate it is likely that the ketoglutarate can pass the blood brain barrier and is utilized.4

Kobayashi and colleagues5 have shown experimentally that after cerebral ischemia there is a marked decrease in the concentration of glutamate in the brain. At the same time there is a small rise in glutamine concentration in the brain. As electrical activity increases during recovery from cerebral ischemia glutamate concentration returns toward normal. These findings agree with those of Folbergrova et al.7 that the decrease in glutamate is associated with the suppression of functional activity. Kobayashi5 suggests that the metabolic changes following ischemia could be due to ammonia detoxification, protein degradation, changes in amino acid transport or to changes in the intermediates of the tricarboxylic acid cycle. These and other studies4 suggest that change induced by ischemia may be reversed by ornithine alpha ketoglutarate.

**Purpose and Design**

The purpose of the trial was to determine the effect of OAKG in patients with recent stroke. The study was double blind and involved 50 patients admitted to the Royal Free and Royal Northern Hospitals, London, with acute stroke. Permission was obtained from the next of kin and, where possible, from the patient. The study was approved by the Ethics Committee of both Hospitals. The patients were given either OAKG 25g daily by intravenous infusion for 5 days or placebo solution in a similar fashion. Neurological assessment was performed before treatment, on the last day of therapy, and 5 days after termination of treatment. Routine medications were supplied as indicated with the exception of vasodilators, osmotic diuretics and steroids.

**Patient selection**

Patients of all ages were included who were admitted within 96 hours of a stroke.

**Exclusion criteria**

Patients were excluded for the following reasons: 1. diabetes, 2. renal failure, defined as a blood urea of over 100 mg %, 3. receiving steroids or vasodilator therapy, 4. having subdural hematoma or subarachnoid hemorrhage.

**Criteria for Withdrawal from the Trial**

Patients were withdrawn for the following reasons: 1. non compliance with protocol for any reason, 2. diabetes, defined as a blood glucose of over 200 mg %, 3. major cardiac dysrhythmias, 4. cardiac failure, 5. renal failure (as previously defined), 6. severe systemic infection, 7. patient or relatives' wish to withdraw from study.

**Administration of the Drug**

Patients were given either a solution of OAKG or placebo. The randomized therapy was performed by the pharmacy staff at the Royal Free Hospital using a conventional sealed envelope technique. For the OAKG solution 25g of ornithine alpha ketoglutarate was dissolved in 500 ml of 5% dextrose. The osmolality of this solution was 0.399. For the placebo solution 25g of anhydrous dextrose was dissolved in 500 ml of 0.225 sodium chloride solution. The osmolality of this solution was 0.355. Both solutions were, therefore, slightly hypertonic. Both solutions were made up freshly each day as the OAKG solution became faintly yellow after 24-36 hours. Also, a set waiting period of 45 minutes from the time a request was made to the pharmacy to the time of delivery of the bottles had to be incorporated into the protocol. (OAKG takes about 20 minutes to dissolve).

**Neurological Assessment**

All patients were subject to neurological evaluation prior to the medication, on the last day of therapy, and 5 days following the termination of therapy. The neurological evaluation scale chosen was based on a paper by Oxbury and his colleagues in 1973.4 Oxbury established that patients particularly at risk were those who were overtly unconscious, those with any combination of impaired consciousness, dense hemiplegia and failure of conjugate ocular gaze toward the side of the limb weakness. These features were therefore heavily weighted numerically. Table 1 gives the details of this numerical evaluation.

**Results**

Data for the 2 groups are shown in tables 2 and 3. A total of 50 patients were studied, 23 were found to be in the placebo group and 22 in the OAKG group (Five patients were lost to the study due to failure of compliance with the protocol). The mean age of the patients was 72 years (SD ± 10 years) and 71 years (SD ± 9 years) for the placebo and OAKG groups, respectively. The blood pressure on admission was similar in both groups (103 ± 3 mm Hg placebo and 105 ± 3 mm Hg OAKG).

---

**Table 1 Grading of Stroke Patients**

<table>
<thead>
<tr>
<th>Level of consciousness</th>
<th>Clinical</th>
<th>Grade</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conscious</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>I</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Drowsy</td>
<td>II</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>Stuporized</td>
<td>III</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>Unconscious</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Purposeful response</td>
<td>IV</td>
<td>30</td>
<td></td>
</tr>
<tr>
<td>Reflex response</td>
<td>V</td>
<td>40</td>
<td></td>
</tr>
<tr>
<td>No response</td>
<td>VI</td>
<td>50</td>
<td></td>
</tr>
<tr>
<td>Limb Power (voluntary)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Against resistance</td>
<td>I</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Against gravity</td>
<td>II</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>Gravity eliminated</td>
<td>III</td>
<td>9</td>
<td>9</td>
</tr>
<tr>
<td>Flicker</td>
<td>IV</td>
<td>12</td>
<td>12</td>
</tr>
<tr>
<td>No movement</td>
<td>V</td>
<td>15</td>
<td>15</td>
</tr>
</tbody>
</table>

| Gaze                   |          |       |       |
| Normal                 | 0        | 0     | 0     |
| Impaired               | I        | 10    |       |
| Deviation              | II       | 20    |       |

**Total possible score** 100
The mean initial neurological impairment score (T0) was also similar in the placebo and OAKG groups (31.9 ± 4.9 for the former and 33.6 ± 4.3 for the latter.)

Four deaths occurred in each group; however, in the OAKG group only 2 occurred during the treatment period, whereas all 4 died within the first 5 days in the placebo group.

Calculation of the means and standard errors at T = 0, T = 5 and T = 10 shows that there is now no longer any difference between the score of the control group had improved to such an extent that there was now no longer any difference between the treatment group and the control. Overall, therefore, the compound appeared to cause initial improvement. This improvement with OAKG was maintained through to day 10. Improvement with placebo was far less dramatic. Even the T0-T10 value does not quite reach the 5% significance level. The figures for gaze disturbance were not large enough to merit separate analysis.

**Discussion**

As might be expected, in both groups of patients there was a considerable variability in stroke severity. The variable natural history of acute cerebral infarction makes drug treatment very difficult to evaluate. However, the initial mean neurological deficit scores were similar in both groups. Moreover, OAKG–treated patients show a considerable and significant improvement by the fifth day. In the control group there was a much smaller change. Overall improvement was not sufficiently large or consistent for a statistically significant difference to be seen. At this stage there were 2 deaths in the treatment group and 4 in the control. Overall, therefore, the compound appeared to cause initial improvement. This improvement with OAKG was maintained over the next 5 days. However, by the 10th day, the score of the control group had improved to such an extent that there was now no longer any difference between the groups. There were the same number of deaths by day 10 (i.e. 4) in both groups.

It appears from table 3 that the main improvement in score on OAKG is, in fact, principally due to an improvement in the level of consciousness score rather than any ma-
jor change in limb power. One must bear in mind, however, that this may, in part, reflect the weighting given to consciousness disturbance in the scoring system and the fact that changes in consciousness may be easier to grade accurately than changes in limb power. If patients who were unconscious on admission are excluded from the score the improvement in score on drug at day 5 is seen to be of major importance.

Unconscious patients, thus, do not respond as well to OAKG. This should occasion no surprise since patients who have sustained massive cerebral infarction are unlikely to respond to any therapeutic endeavor.

To determine whether the drug has a long term beneficial effect many more patients would need to be studied. It would also be of interest to prolong the infusion period. The initial improvement is unlikely to be due to an osmotic effect of the drug although, of course, the solution is hypertonic to plasma. The control solution is also hypertonic. Decrease in brain edema, however, could well be achieved by other mechanisms. The sodium pump could be adversely affected by a decrease in concentration of glutamate in brain tissue. The improvement must, in any event, result from the drug although, of course, the solution is hypertonic to plasma. The control solution is also hypertonic. Decrease in brain edema, however, could well be achieved by other mechanisms. The sodium pump could be adversely affected by a decrease in concentration of glutamate in brain tissue.

### TABLE 3  Total Scores Divided into Components

<table>
<thead>
<tr>
<th>Placebo</th>
<th>Mean score ± SEM</th>
<th>OAKG</th>
<th>Significance of improvement in score</th>
</tr>
</thead>
<tbody>
<tr>
<td>T0</td>
<td>T5</td>
<td>T10</td>
<td>T0-T5 p &lt; 0.025</td>
</tr>
<tr>
<td>Total score</td>
<td>28.4 ± 4.9</td>
<td>24.0 ± 5.7</td>
<td>21.2 ± 4.4</td>
</tr>
<tr>
<td>Level of consciousness</td>
<td>8.2 ± 2.8</td>
<td>7.1 ± 2.7</td>
<td>6.7 ± 2.6</td>
</tr>
<tr>
<td>Limb power</td>
<td>18.0 ± 3.0</td>
<td>17.5 ± 2.8</td>
<td>17.5 ± 2.9</td>
</tr>
</tbody>
</table>

NS: Not significant at 5% level.
difference in score from placebo 5 days after cessation of therapy.

Acknowledgments

We wish to thank Jacques Logesias Laboratories, Paris, for the supply of ornithine alpha ketoglutarate and for financial support. We also wish to acknowledge the help of the nursing staff of the Royal Free Hospital and Royal Northern Hospital, together with the pharmacy at the Royal Free Hospital.

References


Effect of Ornithine Alpha Ketoglutarate (OAKG) on the Response of Brain Metabolism to Hypoxia in the Dog


SUMMARY  Hypoxia is well known to cause an increase in brain anaerobic glycolysis. Ornithine alpha ketoglutarate (OAKG) given to six dogs was shown to attenuate these metabolic disturbances caused by hypoxia. Brain oxygen utilization was higher after ornithine alpha ketoglutarate during hypoxia than during a period of hypoxia alone.

BOTH AMMONIA and hypoxia can provoke cerebral anaerobic glycolysis in animals.1 Ornithine alpha ketoglutarate (OAKG) given to patients with hepatic encephalopathy, who also have evidence of cerebral anaerobic glycolysis, causes a fall in cerebral glucose utilization and an increase in oxygen consumption. Similarly, ammonia intoxication in animals can be prevented by pretreatment with OAKG. In patients with hepatic encephalopathy and in animals with experimental ammonia intoxication, OAKG could act by lowering the blood ammonia levels, as suggested by Michel, Oge and Bertrand,2 by bypassing the critical pyruvate decarboxylase stage affected by ammonia. Or it could accelerate the citric acid cycle by replenishing the intermediaries. The fall in cerebral glucose utilization could then be explained by a negative feed-back mechanism from the cycle. We have previously suggested that this could involve CO₂. It is known that elevated CO₂ levels decrease,3 and lowered CO₂ levels increase, glucose utilization by the brain.1 The purpose of this study was to evaluate the effect of ornithine alpha ketoglutarate on the anaerobic glycolysis provoked by hypoxia.

Methods

Six mongrel dogs of mean weight 15 kg (sd ± 2) were anesthetized with sodium pentobarbitone 25 mg/kg body weight. Both femoral veins were cannulated; one for experimental drugs and the other for maintenance doses of sodium pentobarbitone.

The right femoral artery was cannulated and connected to a Bell and Howell blood pressure transducer. Arterial blood samples were also obtained via this cannula. The animals were ventilated through a tracheostomy at constant rate and volume throughout the experiment.

Cerebral Blood Flow

The method for measuring cerebral blood flow was that of Ingvar and Lassen4 using the intra-carotid injection of ßKrypton. The left superior thyroid artery was identified and the common carotid artery was catheterized via this vessel. Cranionomy and cannulation of the superior sagittal sinus were carried out as previously described.5

Sufficient ßKrypton gas, dissolved in 1 ml of 0.9% weight by volume NaCl solution (saline), was injected into the carotid artery to give a constant plateau of radioactivity over the left parietal region for 45 seconds. The changes in cortical radiation were measured with a small Geiger counter placed over the exposed parietal cortex. Cerebral (cortical) blood flow was measured by analysis of the first 100 seconds of the curve after the end of the injection.

Cortical oxygen and glucose consumption were calculated as the product of flow and arterio-venous difference. The superior sagittal sinus in the dog is known to drain blood only from the cortex.7

From the Section of Clinical Pharmacology, Medical Unit, Royal Free Hospital, Pond St., Hampstead, London, NW 3 20G, England.
Controlled trial of ornithine alpha ketoglutarate (OAKG) in patients with stroke.
M L Woollard, R M Pearson, G Dorf, D Griffith and I M James

Stroke. 1978;9:218-222
doi: 10.1161/01.STR.9.3.218

Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1978 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the
World Wide Web at:
http://stroke.ahajournals.org/content/9/3/218

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in
Stroke can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office.
Once the online version of the published article for which permission is being requested is located, click Request
Permissions in the middle column of the Web page under Services. Further information about this process is
available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Stroke is online at:
http://stroke.ahajournals.org//subscriptions/