

The Effect of Tirilazad Mesylate (U74006F) on Cerebral Oxygen Consumption, and Reactivity of Cerebral Blood Flow to Carbon Dioxide in Healthy Volunteers

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Background: The 21-aminosteroids are a series of compounds designed to inhibit lipid peroxidation in the cell, and, as such, may have cerebral protective effects. The current study was performed to evaluate the effect of a 21-aminosteroid, tirilazad mesylate (U74006F), on cerebral blood flow, metabolism, and carbon dioxide reactivity.

Methods: Using a double-blind study design, eight volunteers received tirilazad mesylate, and eight others received only vehicle. The cerebral blood flow was measured by single photon emission computerized tomography using ^{133}Xe inhalation in the resting condition at the beginning of the study and after infusion of tirilazad mesylate (1.5 mg/kg) or vehicle. Cerebral oxygen metabolism was calculated from the cerebral blood flow and the measured cerebral arteriovenous oxygen content difference. After both of the above cerebral blood flow measurements, arterial carbon dioxide tension was decreased by voluntary hyperventilation, and, later, increased by breathing an air/carbon dioxide mixture. The relative changes in cerebral blood flow induced by the Pa_{CO_2} variations were estimated from the changes in the arteriovenous oxygen content difference.

Results: Blood pressure, pulse rate, and Pa_{CO_2} were similar before and after the infusion of tirilazad mesylate in both groups, and there was no difference between the groups. The cerebral blood flow and oxygen metabolism did not change after the tirilazad mesylate infusion. The slope of the regres-

sion line of relative change of estimated cerebral blood flow and Pa_{CO_2} (regression coefficients in both groups, > 0.90) was unchanged after infusion.

Conclusions: Tirilazad mesylate has no effect on cerebral blood flow, cerebral oxygen metabolism, or reactivity of cerebral blood flow to carbon dioxide in healthy volunteers. (Key words: Carbon dioxide, brain: cerebral blood flow; cerebral oxygen consumption; cerebral vascular reactivity. Pharmacology, free radical scavenger: tirilazad mesylate.)

OXYGEN free radicals arise from a number of sources within injured or ischemic tissue.^{1,2} These radicals are highly reactive, and can attack cellular constituents. Unsaturated fatty acids comprising much of the phospholipid environment of cell and organelle membranes are particularly susceptible to the effects of oxygen free radicals or peroxidation. The process of peroxidation and the generation of oxygen radicals have been reviewed extensively.^{1,2}

The 21-aminosteroids are a new series of compounds designed to inhibit lipid peroxidation in the cell. U74006F (tirilazad mesylate), the first member of the series of 21-aminosteroids available for clinical testing, inhibits lipid peroxidation by scavenging lipid free radicals.³ In addition, it has a stabilizing effect on the cell membrane, by blocking the release of free arachidonic acid from the injured cell membrane.⁴ Thus, tirilazad mesylate may have an important role in the treatment of cerebral ischemia and vasospasm. Results from animal studies have been promising,⁵⁻⁷ but a place for these drugs in the treatment of human disease awaits outcome trials that are currently in progress.

Because tirilazad mesylate is a potentially useful drug in neurologic intensive care, it is important to know its effect on cerebral blood flow (CBF), cerebral oxygen metabolism (CMR_{O_2}), and reactivity of cerebral blood flow to changes in arterial carbon dioxide tension (carbon dioxide reactivity).

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Materials and Methods

Sixteen healthy male volunteers were included in the study, which was approved by the Scientific Ethical Committee. Informed consent, according to the Helsinki II declaration, was obtained from each participant. Eight volunteers, with a median age of 23 yr (range 20–30 yr) were assigned to group A (receiving tirilazad mesylate), and eight others, with a median age of 25 yr (range 20–31 yr), were assigned to group B (receiving vehicle only). One volunteer in group A was excluded because of malfunction of the jugular catheter. The volunteers fasted and did not smoke for at least 12 h before the study.

Before the volunteers were included in the study, it was ensured that their hemoglobin, hematocrit, leukocytes and differential count, thrombocytes, creatinine, glucose, albumin, protein, creatine kinase, bilirubin, basic phosphatase, glutamyl-transferase, alanin-aminotransferase, lactat-dehydrogenase, carbon dioxide, calcium, phosphate, sodium, potassium, and ECG were normal, and that their urine was free of protein, glucose, ketones, and hemoglobin.

Study Design

The study was prospective, randomized, and double blind. Blood and urine samples were, again, collected for the same tests mentioned above, after which three sets of arteriovenous blood samples were drawn (baseline), followed by an absolute regional CBF measurement using ^{133}Xe inhalation. During this measurement, one additional set of blood samples was collected. Then, the arterial carbon dioxide tension (Pa_{CO_2}) was decreased by voluntary hyperventilation, and, later, was increased by breathing an air/carbon dioxide mixture. The relative changes in CBF, induced by the Pa_{CO_2} variations, were estimated from changes in the cerebral arteriovenous oxygen content difference (AVDO_2). After a pause of 50 min, group A received tirilazad mesylate, and group B received vehicle. When the infusion was finished, blood sampling, CBF measurement, and carbon dioxide manipulations were repeated.

Catheterization, Monitoring, and AVDO_2 Measurement

Under local anesthesia, a plastic cannula was introduced into the left radial artery, and a catheter was placed in the right internal jugular vein, with the tip in the jugular bulb. The correct position of the catheter

was tested by injecting isotonic saline into the catheter, and confirmed by a typical murmur in the subject's ear.⁸ An intravenous catheter was placed in the brachial vein for the infusion of tirilazad mesylate or vehicle.

The mean arterial blood pressure (MABP) was continuously invasively measured *via* the cannula in the radial artery. During the study, ECG and pulse rate were also monitored.

All sets of blood samples consisted of one arterial and two venous blood samples (mean value used for calculations) that were drawn simultaneously from the radial artery catheter and jugular catheter, respectively. The blood was analyzed immediately for hemoglobin and hemoglobin saturation (OSM3 Hemooximeter, Radiometer, Copenhagen), oxygen tension, carbon dioxide tension, and pH (ABL3, Radiometer, Copenhagen).

Measurement of Absolute Regional CBF

During CBF measurements, the volunteers rested in quiet surroundings in the supine position and with eyes closed. ^{133}Xe inhalation and single photon emission computerized tomography (SPECT) (Tomomatic 64; Medimatic, Hellerup, Denmark) of the brain were used for measurement of regional CBF. For the estimate of arterial ^{133}Xe input to the brain, a detector over the apex of the right lung was used. The scanner yielded three parallel slices at 1, 5, and 9 cm above the orbitomeatal (OM) plane.^{9,10} The global CBF was estimated from the OM 5 plane as the mean of all brain pixel values.¹¹ Regional CBF was estimated by a standardized set of symmetrically placed regions of interest. A side-to-side asymmetry ratio of less than 10% was considered normal.¹²

The second CBF (SPECT) was corrected for any difference of Pa_{CO_2} between the first and second CBF measurement using the carbon dioxide reactivity for each volunteer (calculated from a semilogarithmic plot of $1/\text{AVDO}_2$ and Pa_{CO_2} [see below]).

Calculation of CMR_{O_2}

During the CBF measurement (SPECT), one set of blood samples was drawn to determine AVDO_2 and Pa_{CO_2} . The AVDO_2 was calculated as the difference between arterial and venous oxygen content (O_2 saturation $\times 1.34 \times$ hemoglobin concentration [g/100 ml] + O_2 tension (mmHg) $\times 0.003$ for arterial and venous blood, respectively). CMR_{O_2} was calculated as $\text{CBF} \times \text{AVDO}_2$.

Calculation of the Carbon Dioxide Reactivity

Initially, a baseline AVDO_2 and Pa_{CO_2} were calculated

Table 1. Baseline Mean Arterial Blood Pressure (MABP), Heart Rate (HR), and Arterial Carbon Dioxide Tension (P_{aCO_2}) before and after Infusion of Tirilazad Mesylate (Group A) or Vehicle (Group B)

	Group A (n = 7)	Group B (n = 8)
Before infusion		
MABP (mmHg)	91 (79–100)	90 (81–103)
HR (beats/min)	65 (62–86)	68 (53–80)
P_{aCO_2} (mmHg)	38 (33–41)	40 (32–46)
After infusion		
MABP (mmHg)	87 (79–103)	90 (84–106)
HR (beats/min)	71 (57–77)	63 (55–76)
P_{aCO_2} (mmHg)	38 (34–40)	40 (35–45)

Values are median (range). There was no statistically significant difference between values before and after infusion or between groups.

as the mean value of three sets of blood samples, and were used as reference levels for the following carbon dioxide manipulations. The volunteers were asked to hyperventilate slightly for 3 min, and maximally for another 3 min. Blood samples for determination of $AVDO_2$ were drawn at 1.5, 3, 4.5, and 6 min after the start of the hyperventilation. The volunteer rested for 10 min, before starting to breathe air with 4% CO_2 for 3 min, and air with 7% CO_2 for another 3 min, to increase P_{aCO_2} . For determination of $AVDO_2$ values during increased P_{aCO_2} levels, blood samples were drawn at 1.5, 3, 4.5, and 6 min after the start of the carbon dioxide breathing.

Relative changes of global CBF induced by carbon dioxide manipulations were estimated by the changes in the $AVDO_2$.¹³ A relative CBF value ($1/AVDO_2$) was calculated from baseline $AVDO_2$, which was expressed as 100%. Assuming a constant CMR_{O_2} during the P_{aCO_2} manipulations (see discussion), determination of changes in $1/AVDO_2$ gives a good estimate of changes in global CBF (according to $CBF = k \times 1/AVDO_2$).¹⁴

In each individual, the correlation of $1/AVDO_2$ (%) and $\log 1/AVDO_2$ with P_{aCO_2} were analyzed using the Pearson product-moment correlation coefficient (r) by linear regression. The slope of the regression line (*i.e.*, the percentage change of estimated CBF [$1/AVDO_2$] per mmHg change of P_{aCO_2}), was used as the carbon dioxide reactivity.

Tirilazad Mesylate/Vehicle

Group A received, over 10 min, 1.5 mg/kg tirilazad mesylate (Upjohn Company, Denmark). The concen-

tration of tirilazad mesylate, which was dissolved in a citrate solution, was 0.75 mg/ml. The volunteers in group B received only the citrate vehicle. The tirilazad mesylate solution or vehicle were delivered in sealed bottles marked only with the randomization code.

Statistics

The values of CBF (SPECT), CMR_{O_2} , and carbon dioxide reactivity, before and after infusion of tirilazad mesylate, respectively, were compared by the nonparametric Wilcoxon rank-sum test for paired sample observations. To evaluate differences between groups (A and B), the Wilcoxon–Mann–Whitney test for two independent groups was used. Differences were considered statistically significant when $P < 0.05$. The results are presented as medians, with the range in brackets.

Results

There was no significant difference between the groups in regard to sex or age. The results of the study are summarized in the tables.

Group A (Tirilazad Mesylate)

The MABP, pulse rate, and P_{aCO_2} did not change after tirilazad mesylate infusion (table 1). The CBF (measured by SPECT) and CMR_{O_2} were unchanged after the infusion (table 2). The carbon dioxide reactivity (calculated from the semilogarithmic plot of $1/AVDO_2$ vs. P_{aCO_2} , as this had a higher regression coefficient than the linear plot, see below) for each volunteer was used

Table 2. Cerebral Blood Flow (CBF) ($ml \cdot 100 g^{-1} \cdot min^{-1}$) and Cerebral Oxygen Metabolism (CMR_{O_2}) ($ml \cdot 100 g^{-1} \cdot min^{-1}$) before and after Infusion of Tirilazad Mesylate (Group A) and Vehicle (Group B)

	Group A (n = 7)	Group B (n = 8)
Before infusion		
CBF	62 (44–79)	54 (45–68)
CMR_{O_2}	4.4 (3.3–5.2)	3.7 (3.2–4.8)
After infusion		
CBF	59 (50–67)	51 (42–71)
CBF_{cor}	59 (40–69)	53 (34–74)
CMR_{O_2}	3.5 (3.1–5.2)	3.7 (2.5–4.8)

Values are median (range). There was no statistically significant difference between values before and after infusion or between groups.

CBF_{cor} = the second CBF corrected for minor differences in P_{aCO_2} between the first and second CBF determination.

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to correct the second CBF (SPECT) for any difference of Pa_{CO_2} from the first CBF measurement (table 2). A statistically significant correlation of $1/\text{AVDO}_2$ and Pa_{CO_2} was obtained over the entire range of Pa_{CO_2} values, both before and after the infusion, whether using a linear or semilogarithmic plot (table 3). Figure 1 shows the regression lines calculated from values before and after tirilazad mesylate infusion, respectively. One person in this group had pain at the site of infusion, and it was necessary to reduce the infusion rate.

Group B (Vehicle)

As in group A, MABP, pulse rate, and Pa_{CO_2} were unchanged after infusion of the citrate vehicle (table 1). Furthermore, CBF and CMR_{O_2} were unchanged after the infusion (table 2). A statistically significant correlation of $1/\text{AVDO}_2$ and Pa_{CO_2} was also obtained in this group. The carbon dioxide reactivity was not changed by the infusion of vehicle (table 3). Figure 2 shows the regression lines calculated from values before and after placebo infusion, respectively. One person in this group had some pain and edema at the site of infusion.

Comparison of Group A and B

The MABP, pulse rate, and Pa_{CO_2} were not different in the two groups. There was no statistically significant difference between group A and B in regard to CBF, CMR_{O_2} , or the carbon dioxide reactivity before and after the tirilazad mesylate or vehicle infusion, respectively.

The semilogarithmic plots yielded the best fit to the individual carbon dioxide reactivity curves, the median regression coefficient being between 0.95 and 0.97 in

Table 3. The Cerebrovascular Carbon Dioxide Reactivity Expressed as Percent Change in Cerebral Blood Flow (Estimated from Changes in AVDO_2) per 1 mmHg Change Pa_{CO_2}

	Group A (n = 7)	Group B (n = 8)
Before infusion		
CO _{2lin}	5.2 (3.7–8.9)	4.8 (4.4–6.2)
CO _{2log}	5.0 (4.6–6.2)	5.2 (4.6–5.7)
After infusion		
CO _{2lin}	5.2 (4.1–6.4)	5.0 (4.1–9.1)
CO _{2log}	4.8 (4.1–5.7)	5.2 (4.6–6.8)

Values are median (range). There was no statistically significant difference between values before and after infusion or between groups.

CO_{2lin} = the median value of linear plots of CBF versus Pa_{CO_2} ; CO_{2log} = the median value of the semilogarithmic plots of CBF versus Pa_{CO_2} .

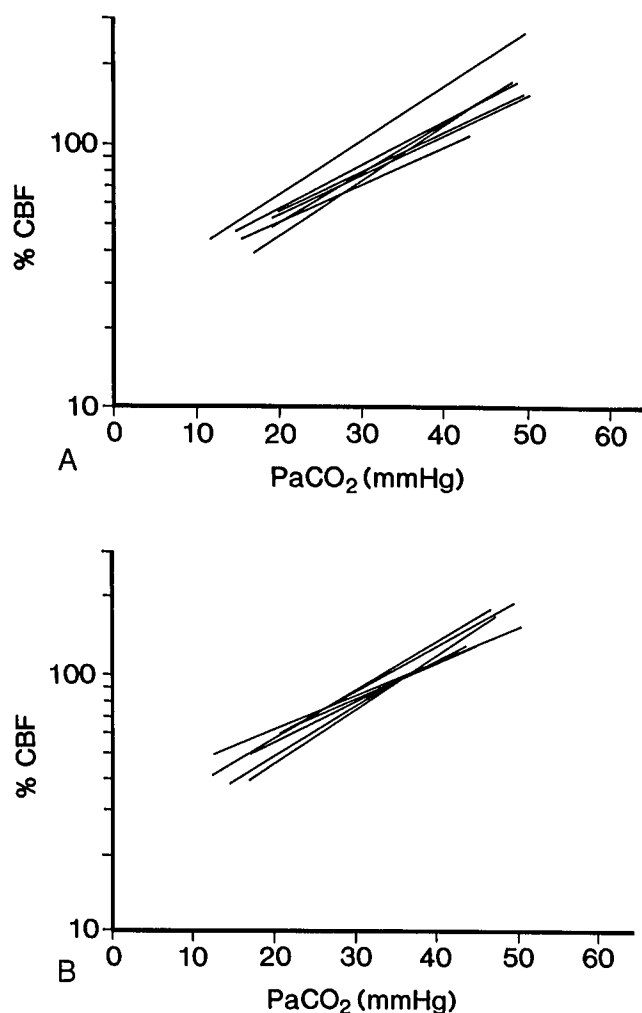


Fig. 1. Regression lines (semilogarithmic plot) of the estimated relative cerebral blood flow (CBF) versus arterial carbon dioxide tension (Pa_{CO_2}) in group A before (A) and after tirilazad mesylate infusion (B).

the two groups before and after the infusion. The linear plots, however, were almost as good, the median regression coefficient being between 0.90 and 0.93.

The median value of the lowest Pa_{CO_2} values measured was 17 mmHg before and after infusion in both groups. The median value of the highest Pa_{CO_2} was 50 mmHg before, and 47 mmHg after, tirilazad mesylate, and 55 mmHg before, and 52 mmHg after, vehicle. The range of the Pa_{CO_2} values for the individual volunteers can be read from figures 1 and 2.

No changes in hematology, blood chemistry, or urine analysis followed the administration of tirilazad mesylate.

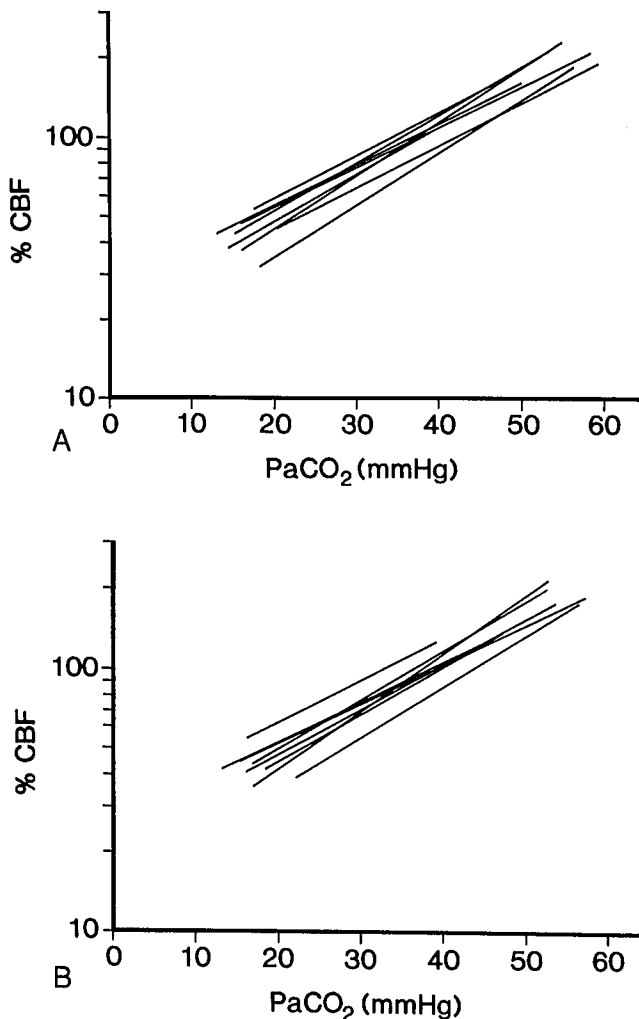


Fig. 2. Regression lines (semilogarithmic plot) of the estimated relative cerebral blood flow (CBF) versus arterial carbon dioxide tension (P_{aCO_2}) in group B before (A) and after vehicle (B).

Discussion

The method of estimating changes in global CBF from changes in $AVDO_2$, assuming a constant cerebral metabolism, is well established.^{14,15} The validity of the $AVDO_2$ method used in the current study requires that oxygen metabolism is constant during manipulations of the arterial carbon dioxide tension. This condition

seems to be fulfilled, because several authors found CMR_{O_2} unaltered by voluntary hyperventilation.¹⁶⁻¹⁹ Studies in awake^{17,20} or anesthetized humans²¹ showed that increases in P_{aCO_2} to 45–60 mmHg are accompanied by increases in CBF at an unchanged CMR_{O_2} , as discussed by Siesjö.²² In the current study, neither CMR_{O_2} nor $AVDO_2$ was changed by either infusion of tirilazad mesylate or placebo.

The shape of the CBF/ P_{aCO_2} relationship has been described as an S-form curve with the steepest slope between 25–60 mmHg. According to Olesen *et al.*,²³ the relationship between CBF and P_{aCO_2} is exponential in this interval. However, there is no uniformity of opinion on the relationship with regard to this physiologic range.¹⁵ Therefore, we choose to use both linear and exponential calculations (the correlation of P_{aCO_2} with both $1/AVDO_2$ and $\log 1/AVDO_2$) and use the best-fitting curve.

The reproducibility, in normal volunteers, of the method of ^{133}Xe inhalation used has been studied with a CBF measurement and three remeasurements within 1 day. No CBF fluctuations occurred during the 3-h observation period.²⁴ One might object that the carbon dioxide manipulations in the first part of the study could influence the second part (*e.g.*, inducing a certain degree of hyperemia). Because, however, 1 h separated the two parts of the study, this is not likely. The similar CBF measured by SPECT before and after placebo confirms this.

The results of the current study show that tirilazad mesylate does not influence CBF, CMR_{O_2} , or the cerebrovascular carbon dioxide reactivity. However, the small number of volunteers in the two groups implies a relatively low power ($1-\beta$) of the statistical test. Given an influence of tirilazad mesylate on CBF of 30%, or on the carbon dioxide reactivity of 20%, the power would be about 90%. Thus, effects of a magnitude with clinical relevance, in all likelihood, would be revealed by the current study, whereas the number of volunteers is not sufficient to find minor effects of tirilazad mesylate.

The reduction in CBF that occurs in response to hypocapnia is used to decrease intracranial pressure during surgery and in the intensive care unit. Accordingly, the impact of drugs on the cerebrovascular carbon dioxide reactivity has important implications when used in these situations. A nonstimulating effect on the cerebral metabolism is also essential for a drug used in neurointensive care as a treatment of cerebral ischemia. The results obtained in the current study, how-

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ever, may not be the same as in a study of patients with injuries of the brain and spinal cord, ischemic cerebrovascular disease, or cerebral ischemia, and further studies are needed to determine whether tirilazad mesylate has a therapeutic role in these categories of patients.

We conclude that tirilazad mesylate, administered to healthy volunteers, has no major effect on global or regional CBF, CMR_{O_2} , or the reactivity of the cerebral vessels to changes in PaCO_2 .

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