Comparative Effects of Chloralose Anesthesia and Sernylan Analgesia on Cerebral Blood Flow, CO₂ Responsiveness, and Brain Metabolism in the Baboon

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SUMMARY A comparison was made between the effects of two different anesthetics, alpha-D-glucos-chloralose and 1-1-phenylcyclo-hexyl piperidine hydrochloride (Sernylan®), on cerebral blood flow (CBF), brain metabolism and cerebrovascular CO₂ responsiveness in primates.

The experiments were carried out on immobilized and artificially ventilated baboons. Anesthesia was induced either with 100/mg/kg chloralose (i.p.) or with 1 mg/kg Sernylan (i.m.). CBF in 8 different brain regions was measured by the intraarteral ⁴⁷Xe clearance technique. The CO₂ responsiveness of the cerebrovascular bed was tested by a gas mixture containing 5% CO₂.

Chloralose depressed total as well as regional CBF compared to the effect of Sernylan. A significant shift occurred toward lower CBF values in the grey matter while white matter flow was identical in the two groups. Brain O₂ consumption was significantly higher during Sernylan anesthesia (3.35 ± 0.34 ml/100 g/min) than during chloralose anesthesia (2.42 ± 0.22 ml/100 g/min). There were no differences in glucose uptake, lactate and pyruvate production, or in arterial and cerebral venous blood gases in the two types of anesthesia. The cerebrovascular CO₂ sensitivity of the Sernylan-treated baboons was higher than that of the chloralose-anesthetized animals, in both the grey and white matter.

Since the early works of Alexander and Cserna, Schmidt and Hendrix, Jowett and others, it is well known that anesthetic agents have common basic features in their cerebrovascular hemodynamic effects. These agents affect the tone of the smooth muscle of the cerebral vessels, as well as alveolar ventilation, blood gas tensions and arterial blood pressure.

In spite of their common features anesthetics with different chemical structures can induce a wide variety of cerebrovascular and metabolic reactions. This must be borne in mind when interpreting the results of clinical and experimental studies of cerebral hemodynamics and metabolism.

It is often difficult to compare studies of anesthetics and brain blood flow and metabolism because of differences in methodology and species. Only those results obtained under standardized experimental conditions in the same species can be compared.

One of the long-used experimental anesthetics is chloralose, which is one of the general anesthetic agents that contains Cl in its structure. Though there are several excellent papers and reviews which discuss its hemodynamic effects no detailed study has so far been published concerning the effect of chloralose on regional cerebral blood flow (rCBF).
In addition, data concerning its cerebrovascular effects on primates are scanty.

In the present study the effects of chloralose and Sernylan on cerebral vessels were compared in baboons. Our aim was to gain a better understanding of the cerebrovascular effects of a widely used general anesthetic and to compare these effects with those of a newer neuroleptic analgesic in primates.

Methods

The experiments were performed on 14 baboons of both sexes, weighing 8–14 kg. One group (6 animals) was anesthetized with 100 mg/kg i.p. chloralose, and the other group (8 animals) was given 1 mg/kg i.m. Sernylan. Both groups were paralyzed with gallamine triethiodide. Respira- tion was controlled by a respirator (Dual Phase Control Pump, Harvard Apparatus, Millis, Mass.) and the end-tidal CO2 content was monitored continuously with an infrared CO2 analyzer (Beckman Instruments, Inc., Fullerton, Calif.). Heparin was given in a dose of 5 mg/kg i.v. to prevent blood clotting. The temperature of the baboons was maintained constant at 37°C by using an infrared lamp regulated by a thermometer (Tele-Thermometer, YSI Instrument Co., Inc., Yellow Springs, Ohio).

The femoral vein was catheterized for infusion of drugs and the femoral artery for blood sampling and for measuring arterial blood pressure. A catheter was inserted into the superior sagittal sinus in order to measure cerebral venous pressure and to obtain blood samples. Arterial and cerebral venous pressure, ECG and CO2 content in the expired air were monitored continuously on a polygraph (Hewlett Packard Co. Medical Electronics Div., Waltham, Mass.). Arterial and cerebral venous blood samples were analyzed for PO2, pH, PO2 (Micro-Astrup Analyzer, Radiometer, Copenhagen, Denmark), O2 saturation, hemoglobin, Os content (Co-Oximeter, Instrumentation Laboratories Inc., Lexington, Mass.), hematocrit (Microhematocrit Centrifuge, Measuring and Scientific Equipment Ltd., London, England) as well as for glucose, lactate and pyruvate (enzymatic method, Biochemical Test Combination, Boehringer Mannheim, New York, N.Y.).

The head of the animal was fixed in a stereotaxic headholder. Regional cerebral blood flow was measured by injecting Xe dissolved in saline into a branch of the external carotid artery through a cannula inserted into a branch of the external carotid artery. Analysis of the 20 min clearance curves was performed with a small laboratory computer (LINC-8 Digital Equipment Corp., Maynard, Mass.) as previously described. The mean flow in the 8 regions of brain was determined by stochastic analysis. The regions in which these measurements were made are shown in figure 1. The flow of the grey and white matter in these regions was calculated by compartmental analysis. Mean hemispheric blood flow was determined by calculating the arithmetic mean of the stochastic flow values of the 8 regions.

Cerebral oxygen consumption, glucose uptake, and lactate and pyruvate production were calculated by multiplying the mean cerebral blood flow (CBF) value by the arteriovenous differences of these substances.

The rate and volume of respiration were adjusted so as to stabilize the initial blood gas values within the normal range. The animals were ventilated with 30% O2 in N2. After control CBF and cerebral metabolic determinations were made the inspired gas was changed to 5% CO2 and 30% O2 in N2. The CBF and cerebral metabolic measurements were repeated after a period of at least 15 min had elapsed to ensure that a new steady state had been attained.

Statistical analysis was performed using Student’s t-test. Effects on General Hemodynamics and Cerebral Blood Flow

Table 1 shows the general hemodynamic and CBF data. Since neither systemic arterial pressure nor cerebral venous pressure was different, cerebral perfusion pressure was the same with the two substances. Arterial hemoglobin content and hematocrit, factors affecting the oxygen capacity and viscosity of the blood, did not show any difference in the two experimental series. Heart rate was significantly higher in the baboons receiving chloralose.

Mean CBF under chloralose anesthesia was significantly lower than under Sernylan analgesia due to the marked difference in cerebrovascular resistance. Mean CBF was higher in all 8 brain regions studied, the difference being significant in 6 (table 2).

Since mean CBF and cerebrovascular resistance as well as the regional stochastic flow were markedly different with the two types of material, a compartmental analysis of rCBF was also undertaken in order to determine how much the cerebral grey and white matter were affected by these differences.

Blood flow and cerebrovascular resistance in the white matter were almost identical during Sernylan and chloralose anesthesia (blood flow: 15 ± 1 and 16 ± 2 ml/100 g/min respectively, p < 0.9; cerebrovascular resistance: 6.71 ± 0.43 and 8.02 ± 1.19 R.U. respectively, p < 0.3). On the other hand, there was a marked difference between the two groups in the grey matter flow and resistance (blood flow: 55

**Figure 1.** Areas from which rCBF measurements were obtained.
Effects on Cerebrovascular CO2 Responsiveness

To analyze the CO2 responsiveness of the cerebrovascular bed, mean CBF values obtained from the two groups were plotted against arterial Pco2. Figure 2 shows the least squares best fit regression lines with 95% confidence limits. There was a significant correlation (p < 0.001) between mean CBF and Paco2 in both groups, however, the slope of the regression line was significantly steeper in the Sernylan-treated group. The CBF sensitivity to CO2 was 1.87 ± 0.19 and 4.07 ± 0.46 ml/100 gm/min/mm Hg under Sernylan and chloralose respectively.

Differences in the cerebral grey matter. Inferior frontal-temporal (regions E and H, fig. 1) grey matter shows the most marked difference between the two series of baboons can be explained by the blood flow differences in the cerebral grey matter. Inferior frontal-temporal (regions E and H, fig. 1) grey matter shows the most marked difference between the two types of materials. Blood flow to the white matter is approximately equal in the two groups.

Since there was no difference between the two series in cerebral perfusion pressure or arterial and cerebral venous blood gases, one can assume that the decreased CBF is a result of depressed cerebral metabolism, caused by chloralose anesthesia. Basal metabolism of chloralose-anesthetized animals has been shown to be significantly lower in the cerebral grey matter. Inferior frontal-temporal (regions E and H, fig. 1) grey matter shows the most marked difference between the two series of baboons can be explained by the blood flow differences in the cerebral grey matter. Inferior frontal-temporal (regions E and H, fig. 1) grey matter shows the most marked difference between the two types of materials. Blood flow to the white matter is approximately equal in the two groups.
EFFECTS OF CHLORALOSE & SERNYLAN ON CBF/Sándor et al. 435

TABLE 4

<table>
<thead>
<tr>
<th></th>
<th>Sernylan</th>
<th>Chloralose</th>
<th>P</th>
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<tr>
<td>AV_{O_2}</td>
<td>8.6 ± 0.8</td>
<td>9.7 ± 0.7</td>
<td>NS</td>
</tr>
<tr>
<td>CMR_{O_2}</td>
<td>3.35 ± 0.34</td>
<td>2.58 ± 0.19</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>AV Gluc</td>
<td>13.7 ± 3.2</td>
<td>14.6 ± 1.8</td>
<td>NS</td>
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<tr>
<td>GMR Gluc</td>
<td>6.62 ± 1.27</td>
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<td>AV Lact</td>
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<td>-0.296 ± 0.068</td>
<td>NS</td>
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<td>0.13 ± 2.11</td>
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<tr>
<td>CMR Pyr</td>
<td>1.27 ± 0.32</td>
<td>0.69 ± 0.28</td>
<td>NS</td>
</tr>
</tbody>
</table>

AV_{O_2} = arteriovenous oxygen difference, vol per cent; CMRO_{2} = cerebral metabolic rate of oxygen, ml/100 g/min; AVGluc = arteriovenous glucose difference, mg per cent; CMRGluc = cerebral metabolic rate of glucose, mg/100 g/min; AVLact = arteriovenous lactate difference, mM/liter; CMRLact = cerebral metabolic rate of lactate, mM/100 g/min; AVPyr = arteriovenous pyruvate difference, mM/liter; CMRPyr = cerebral metabolic rate of pyruvate, μM/100 g/min.

TABLE 4

than that of awake controls. In the present study CMRO_{2} was significantly lower in the animals that received chloralose. However, cerebral glucose consumption and lactate and pyruvate production were not significantly different in the two experimental series.

Another explanation for the CBF differences under the two types of substances may be the increased sympathetic neural discharge observed with chloralose anesthesia as has been demonstrated by Ludány4 and Arfors et al.5 According to some recent studies26,28 sympathetic neural impulses can decrease CBF without changes in arterial PCO_{2}, pH, or PO_{2} values although the exact mechanism is not known. Though we have no direct evidence, increased sympathetic activity could have occurred in our present experiments, as demonstrated by the significant increase in heart rate in the chloralose-anesthetized baboons.

Chloralose anesthesia has definite advantages over other types of anesthetics in some fields of research. For example, alpha-chloralose has less effect on basal cardiac performance than other anesthetics.21,25 Furthermore, it can be used successfully in studies of the central neural regulation of the cardiovascular system since reflex activity is better maintained.28 It has also been demonstrated that dogs under alpha-chloralose anesthesia of 6 hours duration showed no time dependent effect of anesthesia on mean arterial pressure, cardiac index, oxygen consumption, arterial PCO_{2} or respiratory rate.

In spite of these advantages of chloralose, some of its
other effects have to be considered when planning and evaluating experiments on cerebral hemodynamics. Driggs and Dumke found a decreased respiratory response to carbon dioxide in chloralose anesthesia. In the present study, we observed not only lower CBF values under chloralose anesthesia but also a decreased sensitivity of the cerebral vessels to arterial PCO2 changes.

CO2 responsiveness in Sernylan analgesia was found to be close to the upper limit of the range of responsiveness reported in the literature and was considerably higher than figures obtained in other studies on primates under pentobarbital anesthesia. Chloralose markedly depressed the respiratory of the cerebrovascular bed to arterial CO2. This difference was most marked in the fast flow (grey matter) component. These studies were carried out at arterial PCO2 values between 30 and 80 mm Hg. Studies in which higher levels of arterial PCO2 were examined have revealed a reduction in CO2 sensitivity under chloralose anesthesia but also a decreased sensitivity of the cerebral vessels to arterial PCO2 changes.

Acknowledgment

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References

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