TITLE: CEREBRAL BLOOD FLOW DISTRIBUTION IN THE RAT WITH MIDDLE CEREBRAL ARTERY OCCLUSION DURING DEEP ISOFLURANE VS PENTOBARBITAL ANESTHESIA

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Introduction. Isoflurane (Iso) and pentobarbital (Pento), when administered in sufficient doses, produce a similarly profound depression of cerebral metabolic rate(1). Thus, administration of either agent, prior to middle cerebral artery occlusion (MCAO), would be expected to benefit outcome. Although both drugs have been evaluated, only barbiturates have been demonstrated to protect(2). Amongst differing pharmacologic properties of these two agents, the most obvious are their effects on cerebral blood flow (CBF). This study was therefore designed to compare CBF distribution patterns in rats with or without MCAO receiving either agent in sufficient doses to produce an EEG burst suppression pattern.

Methods. Fasted Sprague-Dawley rats (8-9 weeks) receiving either isoflurane 1.4% (n=13) or i.p. pentobarbital (30 mg/kg) (n=13), were intubated and mechanically ventilated (30% $O_2$/balance $N_2$). Femoral arterial and venous cannulas were placed. A subtemporal craniectomy allowed exposure of the MCA which was ligated with 10-0 suture just distal to the lenticulostriate branch. Prior to MCAO, additional anesthetic in both groups was given to produce and maintain an isoelectric EEG with rare burst activity. In five rats in each group the MCA was not ligated thereby providing sham controls. Mean arterial pressure (MAP) was maintained at 90-100 mmHg with blood infusion, while temperature (36.5-37.5°C), $PaCO_2$ (38-42 mmHg), and $PaO_2$ (110-130 mmHg) were controlled. 30 min after MCAO, $^{14}$C-IAP (75 uCi/kg) was infused i.v. over 45 sec with timed arterial sampling(3). Frozen section generated serial coronal autoradiographs, chosen from standardized sections anatomically served by the MCA, were analyzed for CBF on an image analysis computer system. Both ipsilateral (lesioned) and contralateral hemispheres were quantitated for flow in the neocortex, subcortex, and total hemisphere; a cortical/subcortical (C/S) CBF ratio was also calculated. In addition, areas (pixel units) within each region with flow values below arbitrary thresholds of 10, 20, and 30 ml/100 gm/min were determined. Values (mean ± S.D.) were compared by the Student's t test and 2-way ANOVA.

Results. There were no differences between groups for physiologic values (MAP, $PaCO_2$, $PaO_2$, body weight, or temp) except for plasma glucose (Iso=137±16; Pento=121±15 mg/dL, $p<.05$). As expected, flow was greater in the isoflurane shams when compared to pentobarbital shams in all regions evaluated (Table 1). Similarly, the number of pixel units in each region where flow was <10, 20, or 30 ml/100gm/min was greater in pentobarbital than isoflurane shams ($p<.01$) (Table 2). In the MCAO groups, ipsilateral regional CBF was reduced by the insult during both anesthetics ($p<.01$). However, anesthetic-dependent regional differences persisted, flow remaining higher in the isoflurane group. No difference between MCAO groups was observed with respect to area where flow was less than 10, 20, or 30ml/100g/min in the lesioned cortex, subcortex, or hemisphere, although standard deviations were large. Inspection of C/S ratios revealed a more homogeneous distribution of flow in the Pento vs Iso shams ($p<.05$). This difference was abolished by MCAO, both groups exhibiting a profound reduction in cortical relative to subcortical flows ($p<.01$). In the contralateral hemisphere, no differences in regional flow values were observed between MCAO and sham rats within anesthetic groups.

| | Cortex | Subcortex | Hemisphere | C/S |
|---|---|---|---|---|
| Iso Sham | 145±13* | 167±44* | 157±22* | .89±.13* |
| Pento Sham | 61±17 | 56±13 | 57±13 | 1.07±.05 |
| Iso MCAO | 57±33* | 111±33* | 93±22* | .52±.23 |
| Pento MCAO | 27±11 | 45±13 | 39±12 | .58±.13 |

Table 1. CBF (ml/100 g/min) in the ipsilateral hemisphere for MCAO vs sham rats. Values represent area-weighted averages from 7 sections/rat. *indicates differences ($p<.05$) between anesthetic groups within sham and MCAO categories. Shams:n=5 per group; MCAO:n=8 per group.

| | <10 | <20 | <30 |
|---|---|---|---|
| Iso Sham | 0 | 0 | 44±8 |
| Pento Sham | 245±116* | 775±238* | 2425±1253* |
| Iso MCAO | 4461±3765 | 5353±3984 | 7329±4872 |
| Pento MCAO | 6361±2831 | 8791±3591 | 12057±5865 |

Table 2. Number of pixel units (averaged over 7 sections/rat) within the ipsilateral hemisphere where CBF was less than 10, 20, or 30 ml/100 gm/min. *indicates differences ($p<.05$) between anesthetic agents within sham and MCAO categories.

Discussion. When CBF alone is considered, no adverse effects could be identified for isoflurane in this model. In fact, during MCAO, CBF in the isoflurane group compared to the pentobarbital group remained greater in all regions evaluated. This data suggests that the distinction previously observed(2) between isoflurane and pentobarbital therapy in improving outcome from MCAO cannot be explained by simple CBF distribution effects, and points rather to local flow/metabolism matching phenomena and/or glucose effects(4).

References.

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(4) Kofke et al. Anesthesiology 65:A582, 1986.