Upsala J Med Sci 101: 97–112, 1996

Occurrence of Adenylate Kinase in Cerebrospinal Fluid after Isoflurane Anaesthesia and Orthognathic Surgery

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ABSTRACT

The study objective was, firstly, to investigate whether anaesthesia with induced arterial hypotension would cause leakage of a biochemical marker of neuronal injury, adenylate kinase (AK), into the cerebrospinal fluid (CSF). (Definition: arterial hypotension = mean arterial pressure (MAP) 50-65 mmHg during ≥ 10 min). Secondly, a subgroup of patients was examined with a limited battery of psychometric tests.

Patients, scheduled for orthognathic surgery, were allocated to either hypotension (n=20) or normotension (n=20). Seventeen patients were subjected to psychometry.

Arterial blood pressure was recorded continuously and controlled by adjustments of the administered concentration of the inhalational anaesthetic isoflurane. Fentanyl, an opioid, was given equally in both groups. A lumbar puncture was performed approximately 20 h post-operatively for a CSF sample, later analysed for AK activity. Neuropsychological tests were performed the day before surgery and the fourteenth day postoperatively.

The CSF-AK value was pathologically increased (>0.040 U/L) in 24 patients (65%), of whom 9 were normotensive. There was no significant difference between the CSF-AK values in the hypotensive and normotensive groups, mean values were 0.082 (s.d. 0.051) and 0.066 (s.d. 0.059) U/L, respectively. The overall correlation between the 10 min MAP levels and the CSF-AK values was close to zero. In the pilot neuropsychological investigation some abnormalities were observed, indicating clinically significant adverse effects in four hypotensive patients, of whom two displayed pathologically increased CSF-AK values. At the group level, the correlation between the changes in psychometry and the measured CSF-AK values was poor.

Increases in CSF-AK activities may be a non-specific occurrence in the perioperative interval, possibly indicating an adverse effect on the brain. Arterial hypotension could not be proven to explain the CSF-AK outcome.

INTRODUCTION

An increase in the activity of adenylate kinase (AK) in cerebrospinal fluid (CSF) has been demonstrated in connection with isoflurane-induced hypotensive anaesthesia in 9 out of 10 patients investigated pre- and postoperatively (9). Increased CSF-AK activity has been associated with disturbances of brain cell integrity under different pathophysiological conditions, including meningitis, dementia, brain tumour necrosis, stroke, resuscitation, asphyxia in newborns and open heart surgery (8,10,24,25,28,30,32,33). This is due to a release of the enzyme from the intracellular to the extracellular compartment, with which the CSF is maintained in diffusional equilibrium. Thus, under normal conditions the CSF-activity of this enzyme is zero or very low, <0.040 U/L (28). The previously observed enhanced efflux of AK into CSF in association with isoflurane-induced hypotensive anaesthesia was considered to be due to hypoxic brain cell injury secondary to hypotension (9). However, conflicting reports have been presented concerning the adverse effects of induced hypotensive anaesthesia on the brain (7,13,22,29). These conflicting results may be explained by differences in the technique for induction of the hypotension, different levels of hypotension attained and the definition and diagnosis of adverse effects.

The main purpose of the present study was to confirm the finding of increased CSF-AK activity after isoflurane-induced hypotension during major oral surgery and to verify the proposed relation between the blood pressure level and the CSF-AK activity in a larger group of patients. Hypotension was defined as a mean arterial blood pressure (MAP) of 50-65 mm Hg and normotension as a MAP >65 mmHg. The minimal period of interest for hypotension was considered to be 10 min. As a complement, neuropsychological tests were performed on a subgroup of both hypotensive and normotensive patients aiming at estimating the degree of any adverse mental effects of clinical significance.

PATIENTS AND METHODS

Patients

Following approval by the institutional ethics committee and in accordance with the Helsinki Declaration informed consent was obtained from each patient before inclusion in the study. Forty patients in ASA class I or II, undergoing surgery for the correction of dentofacial deformities with malocclusion of the bite, were randomised into two groups, either receiving anaesthesia with induced hypotension (group H) or with normotension (group N). Preoperatively, the routine serum biochemistry and haematological profile of every patient were checked to be within normal limits.

Anaesthesia

Premedication with morphine 0.1-0.2 mg/kg and scopolamine 4-8 μg/kg was given i.m. one hour before surgery. Fentanyl 0.1-0.2 mg followed by thiopental 5 mg/kg were given to induce anaesthesia. Succinylcholine 1 mg/kg (8 patients) or vecuronium 0.1 mg/kg (32 patients) was given to facilitate nasal intubation. Prior to surgery an additional dose of 0.1-0.3 mg of fentanyl was administered. Anaesthesia was maintained by isoflurane in nitrous oxide/oxygen (70/30). Arterial hypotension was induced prior to surgery by increasing the inspired concentration of isoflurane. Repetitive doses of fentanyl or vecuronium were given as clinically indicated. Other drugs used perioperatively were betamethasone, penicillin, oxymethazoline and lidocaine, 20 mg/ml with adrenaline, 12.5 μg/ml (16). The ventilation was adjusted to keep the end-tidal CO_2 within the range 4.4-5.4 kPa during normotension and 3.4-4.4 kPa during hypotension.

Patient monitoring included pulse oximetry, end tidal CO_2 and the inspired and expired isoflurane concentrations using an Ohmeda 5250 RGM monitor (OHMEDA, Colorado, USA). The gases were sampled from the proximal end of the endotracheal tube. ECG was continuously monitored with a Kontron ECG monitor (Kontron Ind. Ltd., Great Britain). Continuous radial arterial blood pressure measurements were made in all patients, except in one of the group N due to technical problems. This patient was monitored with non-invasive blood pressure measurement. The blood pressure and isoflurane concentration were recorded on a BBC SE 120 recorder (Goerz Metrawatt, Austria) with a paper feed of 30 cm/h. For blood pressure registration an amplitude of 1.25 cm corresponded to 10 mmHg, and the degree of amplification for isoflurane registration was 1% per 1.25 cm. The duration of hypotension was measured from the recorded blood pressure curve. The area under curve (AUC) for the isoflurane concentration, representing the total amount of isoflurane exposure, was estimated from the recording. The individual mean end-tidal isoflurane concentration was calculated by dividing AUC by the time of isoflurane administration.

Surgery

The surgery performed was either a sagittal split of the mandible or a maxillary osteotomy at Le Fort I level, or a simultaneous correction of both jaws (16), [Table 1].

Postoperative care

All patients were extubated in the operating room. They received oxygen, 2 L/min, through a nasal catheter and were continuously monitored by pulse oximetry (Kontron Instruments Ltd., Great Britain). The patients were supervised in the intensive care unit for 20 h. Ringer's lactate, 15 ml/kg, 5 % glucose in saline, 15 ml/kg and 0.5 L dextran 70 were infused during the first 24 h. Lumbar punctures for CSF-AK determination were performed in the morning after the operation, about 20 h after the end of surgery.

Biochemical analysis

0.5 ml of CSF was used for analysis. The samples were immediately chilled with ice and centrifuged twice within 45 min. The clear supernatants were immediately frozen and stored at -70° C until analysis. To exclude contamination from red blood cells, spectrophotometry of all supernatants was performed. This was aiming at detection of haemoglobin and protoporphyrin derivatives by scanning in the wave length range 400-650 nm with a Shimazu Double-Beam Spectrophotometer (Spectronic 200 UVd, Bansch & Lomb Inc., Japan). A light absorbency at 415 nm of more than 0.035 was considered as discriminative for haemoglobin identification.

Psychometry

The last 20 of the 40 patients randomised, 9 from group N and 11 from group H, were included in the psychometric part of the study. Preoperative neuropsychological testing was done the day before surgery in order to acquire a baseline of the patients performance. The postoperative testing was undertaken on the 14th day after surgery. The tests were conducted by a trained neuropsychologist who was not aware to which treatment group the patients were assigned.

Psychometric tests were chosen specifically to estimate different aspects and levels of memory function, since the hippocampal structures of the brain have been reported to be especially sensitive to hypoxia (17,20). A verbal learning task was chosen in order to specifically measure the hippocampal function of the dominant hemisphere (5,19). The test was designed to account for immediate, short and long term memory, respectively. This test also provided a learning curve, revealed learning strategies or their absence and detected tendencies to contamination or confabulation. In order to examine the function of the hippocampal area in the non-dominant hemisphere two parallel design-learning tasks were chosen. The Rey-Osterrieth Complex Figure Test (21,23) and The Taylor Complex Figure Test (18,26,27) were selected because of their sensitivity to measure visuo-spatial memory functions. The Digit-span test in the WAIS-R battery was used in order to determine the immediate memory function and attention (31).

Statistical evaluation

A study population of 36-40 patients was deemed necessary by calculating data from a previous pilot study, and making the assumption of a mean group difference in CSF-AK of at least 0.040 U/L at the 5% significance level and with a statistical power of minimum 80% (9). An unpaired, two-sided t-test was used. Fisher's exact two-sided test was used to evaluate the distribution of pathological and non-pathological values of CSF-AK in the two groups. The Pearson product moment correlation coefficient was calculated between the lowest MAP during 10 min and the CSF-AK activity, and the same test was used to correlate the percent decrease in blood pressure and the CSF-AK value.

Wilcoxon signed rank test was used for comparisons of pre- and postoperative results of the patients in the psychometric part of the investigation. Kendall's rank correlation coefficient was calculated between the CSF-AK values and the differences between pre- and postoperative results from each of the 4 different neuropsychological tests.

If not specifically indicated, the test used for the comparison of demographic data between the study groups was an unpaired, two-sided t-test. For acceptance of statistical significance the 5%-level was chosen. With each mean value the standard deviation is presented within brackets in the tables. In the case of a non-normal distribution of data the median value is presented with the 1st quartile value within parenthesis.

A multiple regression analysis was considered necessary to perform (cf. Results).

RESULTS

Patient characteristics

One patient in group N was excluded from the study because of profuse nasal bleeding after extubation, resulting in cyanosis before reintubation could be performed. Two other patients in group N were unintentionally hypotensive, the lowest 10 min MAP level was 60 and 63 mmHg, respectively, and thereby they were discarded. Thus, 37 patients were analysed in the biochemical part of the investigation. The overall results were not changed if the "intention-to-treat" strategy was used.

Table 1. Some demographical and surgical data.

	Group N (n=17)	**Group H** (n=20)
Number of patients	17	20
Sex, *Male/Female*	7/10	3/17
Age, *years* (median)	31.0 (25.0)	39.5* (30.8)
Weight, *kg* (mean)	69.7 [11.5]	60.2* [10.6]
Height, *cm* (mean)	170.5 [10.4]	167.1 [8.3]
Surgery, type 1	6	10
" " **2**	4	3
" " **3**	7	7

Type of surgery:
1 = Sagittal split of the mandible, 2 = Maxillary osteotomy, 3 = Simultaneous correction of both jaws
* $p < 0.05$
Note: Data are median values (and 1st quartile) or means [and SD].

Sex, height and the type of surgery performed did not differ between the groups H and N (Fisher's exact test for sex and the Chi-square test for the type of surgery) [Table 1]. The age was significantly higher (Wilcoxon rank sum test) and the weight was significantly lower in group H [Table 1]. The duration of anaesthesia, defined as the duration of isoflurane administration, and the dose of fentanyl did not differ between the two study groups [Table 2]. As expected from the method for induction and maintenance of hypotension, the mean and the peak isoflurane concentrations were significantly higher in group H [Table 2].

Table 2. Some pharmacological variables.

	Group N (n=17)	**Group H** (n=20)
Duration of anaesthesia, *min.*	196.2 [49.8]	202.5 [63.3]
Mean isoflurane concentration, %	0.90 [0.20]	1.11* [0.39]
Peak isoflurane concentration, %	1.69 [0.40]	2.30* [0.95]
Fentanyl dose, *mg/kg/h*	2.46 [0.97]	2.57 [0.90]

* $p < 0.05$
Note: Data are means [and SD].

CSF-AK following anaesthesia

Individual data for haemodynamics and CSF-AK values are presented in Table 3. An increased CSF-AK activity of >0.040 U/L was found in 24 of the 37 patients (65%), most of whom were in group H, 15 contra 9. However, the distribution of patients with normal or pathological CSF-AK values did not differ significantly between the groups [Table 4]. The mean CSF-AK activity was 0.066 U/L in group N and 0.082 U/L in group H [Table 4], the intergroup difference being not significant. There was no correlation between the blood pressure levels and the CSF-AK results ($r = -0.05$) or between the CSF-AK results and the AUC for MAP <65 mmHg ($r = 0.06$). Also, the degrees of blood pressure decrease and the CSF-AK activities correlated poorly ($r = 0.18$).

In a multiple regression analysis (Spreadware Statistics Menu for Microsoft Excel), including all demographic- and haemodynamic variables, the multiple correlation coefficient was 0.35, with the mean isoflurane concentration and the fentanyl dose as the only variables with significant b-values. Since the correlation coefficient between the mean isoflurane concentrations and the lowest MAP (10 min) was less than expected ($r = -0.21$) and the corresponding r value between the lowest MAP values and the CSF-AK values was close to zero (-0.05), there was possibly a coupling between the individual mean isoflurane concentrations and the CSF-AK outcome apart from the blood pressure level. In the same way there might be a connection between the fentanyl

doses and the CSF-AK results besides an effect via the blood pressure. The correlation coefficient between the fentanyl doses and the lowest MAP values was also close to zero (0.06).

Table 3. Some haemodynamical data, fentanyl dose, mean isoflurane concentration and CSF-AK activity of each individual.

Patient number	Percent BP-decrease (%)	Lowest MAP (10') (*mmHg*)	Fentanyl dose (μg/kg/h)	Mean isoflurane concentration (%)	CSF-AK (*U/L*)
1	29	77	3.7	0.99	0.071
2	16	66	1.5	1.05	0.048
3	0	89	3.0	0.67	0.032
4	30	72	2.0	1.05	0.055
5	36	70	1.2	0.82	0.016
6	17	71	2.3	0.98	0.032
7	31	81	1.5	0.84	0.055
8	23	67	1.9	0.53	0.071
9	21	77	2.7	1.21	0.257
10	26	67	3.5	0.72	0.040
11	25	75	1.4	0.53	0.040
12	23	78	2.6	0.92	0.024
13	9	74	3.7	0.94	0.087
14	46	65	2.0	0.94	0.111
15	*22*	*63*	*3.0*	*0.60*	*0.040*
16	18	65	2.8	1.07	0.040
17	20	66	1.4	0.80	0.135
18	17	70	4.4	1.15	0.016
19	*40*	*60*	*2.1*	*0.50*	*0.040*
20	37	58	1.8	1.60	0.008
21	37	61	1.5	0.68	0.135
22	47	51	3.6	1.90	0.119
23	38	53	2.8	1.16	0.024
24	32	63	2.5	1.79	0.103
25	50	62	4.8	1.25	0.202
26	19	57	3.7	1.23	0.079
27	38	64	3.3	1.25	0.087
28	30	60	2.1	0.71	0.048
29	38	55	1.5	1.56	0.087
30	23	52	3.1	0.72	0.079
31	33	56	2.5	0.69	0.079
32	25	53	3.7	0.95	0.143
33	16	54	2.5	1.33	0.024
34	41	55	2.3	0.75	0.016
35	39	56	2.3	1.02	0.166
36	42	49	2.2	0.55	0.063
37	47	54	1.9	1.17	0.040
38	53	48	1.5	0.82	0.063
39	50	51	1.7	1.13	0.075

Footnotes to Table 3:
Patients 1-19 = Group N. Patients 20-39 = Group H.
Percent BP-decrease = the percent decrease from the immediate preinduction blood pressure value to the 10 min lowest value.
Lowest MAP = the lowest mean arterial pressure recorded for at minimum 10 min.
CSF-AK = the activity of adenylate kinase in cerebrospinal fluid.

Table 4. The distribution of pathological and non-pathological CSF-AK results and the mean CSF-AK results in the study groups.

	Group N (n=17)	**Group H** (n=20)
CSF-AK ≤ 0.040 (U/L)	8	5
CSF-AK > 0.040 (U/L)	9	15
Mean CSF-AK (U/L)	0.066 [0.059]	0.082 [0.051]

CSF-AK = the activity of adenylate kinase in cerebrospinal fluid, mean [and SD].

The differences in CSF-AK activities were compared between groups with different mean isoflurane concentrations, group mean of 1.0% +/- 1, 2, 3 or 4 S.E.M. (S.E.M. = 0.05%). The mean CSF-AK value was constantly in the order of 30-40% higher in the high dose group and at 1.2% a significant difference was evident. The same procedure undertaken with the fentanyl data revealed no significant differences.

The group average isoflurane concentration in 12 patients with CSF-AK activities >0.080 U/L was 1.19% (0.39) in contrast to 0.93% (0.27) in 25 patients with CSF-AK activities ≤0.080 U/L ($p = 0.02$, unpaired, two sided t-test). The mean intergroup difference in MAP level was just 1.6 mmHg. The same calculations undertaken with the fentanyl data could not reveal significant differencies.

Neuropsychology

The results from the neuropsychological tests are presented in Table 5. Three from group N, of the 20 patients tested, were excluded from this second part of the study because of difficulties of a practical nature in data collection, or unwillingness from patients to complete the postoperative tests. No significant changes were observed in the neuropsychological tests from pre- to post-operative testing for the remaining 17 patients as a group. Furthermore, no correlation was found between the CSF-AK values and the differences in pre- and postoperative neuropsychometry.

Among individual results four patients, all hypotensive, deteriorated significantly from pre- to postoperative testing, they fell below accepted cut-off levels for visuo-spatial memory (21) and verbal memory (consensus the Swedish National Board of Health). One patient, #36, who performed well in the preoperative visuo-spatial test reduced her value of the preoperative test from 23 to 7.5 postoperatively, in spite of good motivation, and in the verbal memory test she passed

the cut off limit of 8 in the postoperative test. She spontaneously complained of reduced capacity. Three patients, #22, #23 and #33, who preoperatively passed the verbal memory test, failed postoperatively. They reduced the recall of words from 8 to 5, from 9 to 7 and from 10 to 6, respectively. The latter patient was followed-up 6 months postoperatively with normalised test result. On this third occasion, she spontaneously complained of difficulties in performing the test. Of these three partly deteriorated patients two, #23 and #33, exhibited normal CSF-AK values (0.024 U/L each), one, #36, had a moderately increased value (0.063 U/L) while in another patient, #22, the CSF-AK value was markedly increased (0.119 U/L). One patient, #17, performed extremely bad in the verbal memory test, but did so in both the pre- and postoperative tests.

Table 5. Individual results from pre- and postoperative neuropsychological tests in relation to the corresponding CSF-AK values.

Patient # according to table 3	Learning factor		Attention span		Figurative memory		Verbal memory		CSF-AK U/L
	pre	post	pre	post	pre	post	pre	post	
5	5	10+	5	7	28	30	9	10	0.016
7	6	4	6	7	25	27	9	8	0.055
8	8	10+	5	4	26	20.5	6	10	0.071
9	5	5	7	8	21	28	9	9	0.257
17	10	10	5	4	7.5	12	5	4	0.135
18	4	3	8	8	19	24	9	9	0.016
20	3	5	5	4	30	28	8	10	0.008
21	10	5	6	5	10	18.5	6	8	0.135
22	10	10	6	6	17	22	*8*	*5*	0.119
23	7	6	8	7	4.5	7	*9*	*7*	0.024
33	4	4	9	9	23	19	*10*	*6*	0.024
34	4	5	8	7	21	19	9	8	0.016
35	4	3	6	6	20	27	10	8	0.166
36	10	2	9	8	*23*	*7.5*	8	7	0.063
37	3	2	7	7	24	23.5	10	10	0.040
38	3	4	7	7	28	21.5	9	10	0.063
39	8	5	6	7	13	6	9	9	0.075

Pre values from the day before surgery; Post values from the 14th postoperative day.
Figurative memory = visuo-spatial memory; Verbal memory = word learning test.
CSF-AK = measured activity of adenylate kinase in cerebrospinal fluid.

DISCUSSION

The CSF-AK results

The present study demonstrates a number of patients with pathological CSF-AK activity (>0.040 U/L). Under other circumstances such an increase would indicate brain injury, since normally the

CSF-AK activity is low, and it should not exceed 0.040 U/L (8,10,24,25,28,30,32,33). The most obvious cause would be low perfusion as a result of induced hypotension. However, this comprehensible hypothesis was not proven in the present study. The mean values of the marker in the two study groups did not differ significantly, and there was no correlation between the blood pressure level or the degree of blood pressure decrease on one hand and the CSF-AK activity on the other hand. Further, one third of the patients with pathologically increased CSF-AK values was normotensive. The result indicates a dysmetabolic event in the CNS, provided hemolysis could be excluded by recording the spectrophotometric absorbency value at 415 nm, Soret's band, being a sensitive marker of haemoglobin (not in table). In 5 cases (# 14, 21, 29, 30 and 35) a small contribution could not be ruled out, and in one case (# 14) a visible stitch-bleeding was evident. If the CSF-AK values of those 5 patients were falsely high, it would further strengthen the suspicion that a low blood pressure did not contribute to the AK release, since 4 of the 5 patients in question were in group H.

A serious objection to the result would be that the definition of the lower limit for normotension, MAP >65 mmHg, was set too low. However, it *was* an intergroup difference also with this design; the 95% confidence interval was 54-58 in group H and 69-75 in group N. Thus, the 10 min lowest MAP periods in the groups were significantly separated.

In comparison with other kinds of surgery high doses of fentanyl were used. This might have lowered the blood pressure in the patients assigned to group N, especially in combination with relatively high concentrations of isoflurane. However, the two discarded patients in group N were unintentionally hypotensive despite low concentrations of isoflurane, mean 0.5 and 0.6 %, respectively, and 0.3-0.4% for both during their hypotensive periods. Also, they were given relatively small or modest doses of fentanyl (2.1 and 3.0 μg/kg/h). Probably, they were more sensitive to the drugs than the average population. The lack of difference between the groups in CSF-AK results was not changed with 19 patients in group N instead of the actual number of 17.

The degree of blood pressure decrease seemed not to play a role. However, we believe that the preanaesthetic pressures were not entirely representative for the individuals, since a reliable preanaesthetic blood pressure would be difficult to define. The blood pressure measurements at the ward lack standardisation in measurements, and the preanasthetic pressure after arrival to the theatre might be influenced either by a heavy premedication or by anxiety, with quite the opposite impact on the pressure. Despite this, if the blood pressure taken before the induction of anaesthesia was used for the calculation of blood pressure decrease, then we were able to state that there was a significant positive correlation between the preanaesthetic pressures and the degree of blood pressure decrease, $r = 0.73$ (not in table), and there was a significant negative correlation between the degree of blood pressure decrease and the lowest pressure levels during

anaesthesia, r = -0.60. But, the correlation coefficient between the degree of blood pressure decrease and the CSF-AK values was just 0.18.

Neither body weight nor age of the patients did correlate significantly to CSF-AK activity, r = 0.14 and -0.16, respectively. Probably, the statistics were not disturbed, to a considerable degree, by the skewed distribution of weight and age.

The clinical significance of the biochemical findings could just be speculated upon. Under other conditions associated with CSF-AK release, the clinical situations are quite different from induced hypotension (8,10,24,25,28,30,32,33). In contrast to our patients, these patients often express obvious mental derangement, e.g. patients with brain tumour or after a stroke incident. In two studies of postoperative sequel following open-heart surgery Åberg et al found that the degree of CSF-AK release correlated with the change in psychometric test results (32,33). It was also found in a control group of pulmonary resections that hardly no release of CSF-AK was registered post-operatively, thereby indicating that anaesthesia and surgery per se would not be obligatory pre-requisites for an increase in CSF-AK activity (33). It seems justified to state that an increased CSF-AK activity reflected a dysmetabolic event of brain cells. The observed extent of CSF-AK release in our extremes was of the same degree as in patients with irreversible injuries in the other studies (8,10,24,25,28,30,32,33).

The lack of relation between the CSF-AK activities and the results of the neuropsychological tests in the current study might be dependent upon the type of brain cell injury and its localisation. If enzyme leakage is supposed to be more of a diffuse phenomenon, minor leakage from several different parts of the brain might result in the same level of CSF-AK activity as major leakage from a restricted area. The psychometric investigations were directed to specific functions in specific brain areas. The hippocampus area with memory function and the boundary areas with e.g. spatial- and verbal skills are thought to be the most vulnerable parts of the brain in a low perfusion situation, as proposed from observations regarding the anatomy of the cerebral vasculature (1,4). If low perfusion has not been the single cause of AK leakage in the present study and if the leakage was more global than focal, then our directed tests would fail to detect adverse changes. However, some deterioration in neuropsychological results was recorded. Since the postoperative tests were performed inasmuch as a fortnight ago from anaesthesia the results must be interpreted as signs of warning. Functional disturbances have been supposed to disappear within a few days to a week after anaesthesia (6,7,11,29). However, Gruvstad discovered slight functional disturbances a year after hypotensive anaesthesia (13).

Other mechanisms behind CSF-AK release

In previous investigations concerning different degrees of hypoxic brain injuries no gross alterations of the blood-brain-barrier (BBB) were found (8,10,24,28,33). In the current study no

indicators of disrupted BBB were analysed. Thus, a BBB alteration cannot be ruled out. With present knowledge, however, we regard such a mechanism as less probable (24).

The surgery itself might have deleterious effects on the brain. The high-frequency sawing would elicit vibrations, probably transferred to the brain causing possible mechanical injury. Such a mechanism might have contributed to an AK-release. However, this theory is highly speculative without any known support in literature.

Although, other mechanisms than hypoxia have to be looked for the strategy of ventilation might be of interest. To prevent extreme cerebral vasodilatation, isoflurane-induced hypotension was combined with a certain degree of hyperventilation. The chosen level of end-tidal CO_2 between 3.4 and 4.4 kPa during hypotension and 4.4-5.5 kPa during normotension might not be the optimum for every patient at every moment. Insufficient hyperventilation might contribute to the pathophysiology (3,12). On the other hand, excessive hyperventilation might result in too low a cerebral blood flow (CBF) at a cerebral perfusion pressure (CPP) of less than 50 mmHg (15). Although, the level of optimal ventilation is considered unknown, the degree of hyperventilation was not extreme and the lower limit of hypotension, of 50 mmHg, was respected with only two exceptions. These patients, # 36 and 38 displayed modestly elevated CSF-AK values of 0.063 U/L (both).

Finally, nitrous oxide might counteract the beneficial isoflurane-mediated reduction of cerebral metabolism, and it would also have the potential to enhance the already increased CBF from isoflurane with at least theoretically adverse effects on CPP (2,14). Since the exposition to nitrous oxide was the same in the groups an impact on the results from nitrous oxide seems improbable.

Conclusions

Confirmatory of a previous study the present work indicated an adverse metabolic effect on the brain in connection with isoflurane-induced hypotension and orthognathic surgery (9). This was indicated by the release of a biochemical marker most probably originating from brain cells into the CSF in 24 of 37 patients (65%), and also indicated by a deterioration in psychometric tests in 4 patients out of 17 (24%) analysed. The hypothesis of a correlation between the degree of lowering of the blood pressure and the degree of release of CSF-AK could not be confirmed. Other mechanisms than induced arterial hypotension have to be looked for. The risk for random significance taken into consideration, it seemed to be a statistical relationship between the individual mean isoflurane concentrations and the CSF-AK outcome worth to explore. However, the relatively low correlation coefficient between the two variables, $r = 0.20$, indicated that this possible relationship was not straight (Figure 1), and obviously a single variable could not explain the CSF-AK result.

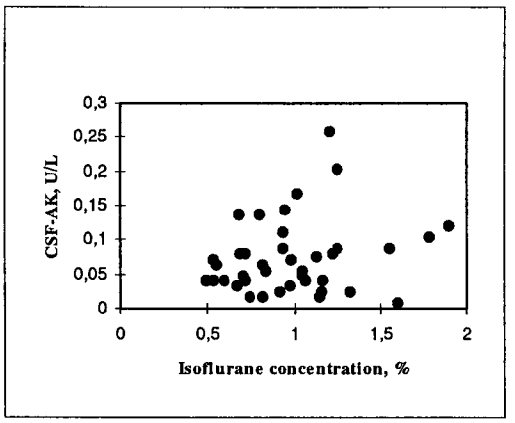

Fig. 1. The non-linear relationship between the CSF-AK values and the individual mean isoflurane concentrations in 39 patients subjected to orthognathic surgery and anaesthetised with isoflurane, nitrous oxide and fentanyl (r = 0.20, n.s.).

ACKNOWLEDGEMENTS

Abbott Scandinavia, BOC Ohmeda Sweden and The County Council of Västmanland, Sweden for grants. Stefan Sörensen, Ph.D., Västerås, Sweden for support with statistics. Dr. Yaw Adu-Gyamfi, MD, Ph.D., Al-Khobar, Saudi-Arabia, Dr. Björn Revenäs, MD, Ph.D., Västerås, Sweden and Prof. Per Hartvig, Pharm D, Ph.D., Uppsala, Sweden for constructive criticism of the manuscript.

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