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Evidence of Cerebral Dysfunction Associated with Isoflurane- or Propofol Based Anaesthesia for Orthognathic Surgery, as Assessed by Biochemical and Neuropsychological Methods

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ABSTRACT

A relationship has previously been described between individual mean isoflurane concentrations and the release of a marker of neuronal injury, adenylate kinase (AK), into the cerebrospinal fluid (CSF) after anaesthesia and orthognathic surgery. Likewise, reduced mental performance has been detected.

Twenty-nine patients scheduled for orthognathic surgery were assigned to isoflurane- or propofol based anaesthesia, which was adjusted to a defined level with the aid of processed EEG and quantitative surface EMG. In the case of a mean arterial pressure (MAP) <50 mmHg a phenylephrine infusion was started to keep the MAP above the minimal level, otherwise no regard was paid to the blood pressure, which never exceeded normal values. A lumbar puncture for CSF sampling was performed approximately 20 h postoperatively. The CSF sample was analysed for AK activity. Neuropsychological tests were performed the day prior to surgery and again in the period 4-8 weeks postoperatively. Five patients were re-examined by psychometry 12-30 months later.

A release of AK into CSF was confirmed, equal in both groups. Correlation with the anaesthetic dose given was poor. Five patients from each group failed significantly in the postoperative neuropsychological tests. They differed in several demographic respects from the others. When five of the failed patients were re-examined 12-30 months later, three patients still performed poorly in the tests.

Biochemical and neuropsychological disturbances were recorded in several patients objected to orthognathic surgery. The underlying mechanisms are unclear, including the role of the anaesthetic drugs or surgery itself.

INTRODUCTION

Circulatory and metabolic stress to the brain may compromise the neuronal integrity, resulting in a release of intracellular compounds to the extracellular space and the cerebrospinal fluid (CSF) (39).

Although not being neurone-specific adenylate kinase (AK) in CSF was found to be a suitable marker of brain cell injury, given that it was sampled and measured under standardised conditions. AK activity is not detected to an appreciable extent, ≤0.040 U/L, in the CSF under normal conditions (18), while an increased activity of this enzyme in CSF has been observed in several different pathophysiological situations (18,38,50,54), among them isoflurane-induced hypotension for orthognathic surgery (14), indicating a disturbed cellular integrity (39,18). Furthermore, a significant correlation has been observed between CSF-AK activity and difference in psychometric score in patients subjected to open-heart surgery (53,54). In general, a patient with increased CSF-AK activity exhibits some mental deterioration, e. g. after a stroke as well as in some instances after open-heart surgery (18,53,54). Clinically, mental deterioration seems not to occur after isoflurane-induced hypotension. However, some patients kept hypotensive for orthognathic surgery deteriorated significantly, as revealed by a psychometric test two weeks postoperatively compared with a preoperative test, while none deteriorated in a normotensive control group (16). Concurrently, the postoperative CSF-AK activity was found to be pathologic in the majority of the patients, 24 out of 37. Nine of the patients with pathologic results were from the normotensive group. There was no correlation between the blood pressure level and the CSF-AK activity. Rather, in a post-hoc analysis, a statistical relationship seemed to exist between the individual mean isoflurane concentrations and the CSF-AK activities regardless of the blood pressure level (16).

The aim of the present study was twofold. Firstly, to detect any statistical relationship between end-tidal isoflurane concentration and CSF-AK activity. Secondly, to examine post-anaesthetic mental performance with an extended battery of pre- and postoperative psychometric tests. The second examination was conducted 4-8 weeks postoperatively, a time at which no residual effects from anaesthesia should occur (4,9,30).

Propofol was used in a control group, since this drug has quite the opposite effect on cerebral circulation, compared with isoflurane (15,17), and since its mode of action, on a subcellular and molecular level, may differ from isoflurane (37). Nevertheless, no preconceived opinion was anticipated, and the study was accordingly descriptive.

PATIENTS AND METHODS

Patients

The study was conducted after approval from the Regional Ethics Committee and in accordance with the Helsinki Declaration. Thirty-two patients, 5 in ASA class II and the rest in ASA I, were included in the study after informed consent. All patients were mentally healthy, without medication acting on the central nervous system, and they had not been anaesthetised during the previous 6 months. They were accepted for major orthognathic surgery. Normal results from routine laboratory tests were obligatory for inclusion.

Anaesthesia - drugs and fluids

A closed envelope technique was used to randomise the patients to one of two hypnotic groups. In Group I anaesthesia included isoflurane, 70% N_2O, fentanyl and alfentanil after thiopental induction. In Group P, propofol was used for both induction and maintenance of hypnosis, while for analgesia the regimen was the same as in Group I, including 70% N_2O. The dosing of either isoflurane or propofol was directed from the individual EEG and EMG responses, and accordingly nor preconceived vaporiser settings nor infusion rates were used (c.f. down). Succinylcholine, 1 mg/kg was given i.v for intubation. No muscle relaxant was used thereafter. Glycopyrrolate, 5 μg/kg was given i.v if the heart rate was less than 50 beats/min.

Peroperatively, a Ringer-acetate solution was infused at a rate of 3-5 ml/kg/h. Postoperatively, a buffered glucose solution, 25 mg/ml, was given. The total 24 h volume delivered was 30-35 ml/kg + 2/3 of the blood loss if exceeding300 mL.

Anaesthesia - monitoring

Maintenance of anaesthesia was directed by the individual responses, as measured by processed quantitative zero crossing frequency EEG (EEG-ZCF) and quantitative upper facial muscle EMG (FEMG) (Datex ABM®, Datex, Finland) (13,33). The following levels of EEG-ZCF and FEMG were chosen as target levels: EEG-ZCF, 5-6 Hz and FEMG, 7-9 units (13,33 and Dr. Markku Paloheimo, Helsinki, Finland, personal communication). The FEMG data presented as "ABM-units" from 0-100 represented 0-15 μV. The same target level was aimed at in all patients.

A bag-in-bottle ventilator, MCM (Dameca A/S, Denmark), and a Mentell circuit (Anmedic AB, Sweden) were used for standard normoventilation (25). The end-tidal CO_2 concentration was measured and kept at 4.5-5.5 kPa. F_iO_2 was at minimum 0.33 to keep the peripheral saturation above 95%. The concentrations of O_2, CO_2, N_2O and isoflurane, as well as the peripheral O_2-saturation, were monitored using a Datex Ultima® (Datex, Finland).

The end-tidal isoflurane concentration was stored digitally every 10^{th} second in a comma-delimited ASCII format. An individual mean isoflurane concentration was calculated, using a Microsoft™ Excel 5.0 program (Microsoft Corporation, USA). The total dose of propofol, delivered and recorded by the Terumo® syringe pump (Terumo Corp, Japan), or in the last 3 patients a BD-Pilot® syringe pump (Becton Dickinson Infusion System, France), was registered, as were the dosages of the opioids given.

The blood pressure was measured using a non-invasive device before and immediately after induction of anaesthesia (Datex Cardiocap®, Datex, Finland). Thereafter, a radial artery cannula was inserted and the Cardiocap® monitor recorded the blood pressure. If the MAP decreased to less than 50 mmHg an infusion of phenylephrine was started to keep the MAP above the minimal level. In the case of an increase in blood pressure associated with an increase in bleeding, >25 mL/min, a nitro-glycerine infusion was started, or, in the case of concomitant tachycardia the ß-blocker metoprolol was given i.v. A three lead ECG was recorded using the Cardiocap®monitor.

Postoperative care

The patients were given nasal oxygen, 2 L/min, and fluids, as described above, and ICU staff supervised them until the first postoperative morning. The technical monitoring included ECG, non-invasive blood pressure, respiratory rate and peripheral O_2-saturation.

Test variables - CSF-AK

A lumbar puncture was undertaken the first postoperative morning, 15-20 h after surgery to receive a 3 mL CSF-sample for subsequent AK activity determination. The handling of the specimen and the determination of AK activity followed procedures previously described (16,18,54). In short, samples were immediately chilled with ice and centrifuged twice, and thereafter stored at −70°C for up to 3 months before analysis. A double-centrifuged CSF sample of 0.5 mL was added to an assay medium buffered with triethanolamine/hydrochloric-acid buffer, pH 7.6, 0.05 mol/L with respect to triethanol-amine. The total volume was 3 mL. AK was assayed by means of auxiliary enzymes terminating in the stoichiometric oxidation of the pyridine nucleotide, with conditions adjusted so that the AK to be measured was rate limiting in the overall reaction. The assay proceeded for at least 20 min in order to give accurate readings. Duplicate controls containing all compounds except the sample were run concomitantly, thereby correcting for the small background activity due to slow physicochemical decay of ATP and possible adenosine diphosphate contamination of the ATP batch. Enzyme activity was expressed in units per litre (U/L) of CSF.

Test variables - Psychometry

As in a previous study, tests were applied measuring the functions of the hippocampus in dominant and non-dominant hemispheres (16). The hippocampal structures are closely related to the storage of memory, verbal and non-verbal, and are known to be sensitive to ischemia (1,3). In the verbal learning test of Luria, the patient is instructed to verbally learn 10 non-related, one- or two syllable words. The patient is asked to repeat these words from his memory immediately after he practised them but also after one and twenty-four hours, respectively. The test is thus designed to measure immediate, short and long term memory. It was also used to provide a learning curve, reveal learning strategies, or their absence, and tendencies to perseveration or confabulation (7,28). The Taylor-Rey-Osterreith test battery of complex figures was chosen to measure visuo-spatial memory functions (27,32,36,44,45). The test consists of a complex figure, which the patient is asked to copy. He is then instructed to remember the figure and after approximately one hour asked to reproduce it from his memory. The Digit-span test from the WAIS-R battery was used in order to determine the immediate memory function and attention level (51). The patient is instructed to immediately repeat a sequence of digits, where the digit span increases up to a point where the patient fails. Hence, the functions tested were: immediate, short and long-term memory for verbal and visuo-spatial modalities and learning structure. The tests were performed once the day before surgery and once in the period 4-8 weeks postoperatively. A skilled neuropsychologist performed and evaluated these tests without knowledge of the patients' group assignation. Scoring of the

Taylor figure was done according to the format by Spreen and Strauss (42). When scoring the drawings of the Complex Figure tests we followed the standard used by the Montreal Neurological Institute (Dr. Marilyn Jones-Gotman, personal communication) and scored strictly. These tests were also evaluated by a hired expert, who was unaware of the kind of patients involved or the interventions undertaken - the only information given was that the material consisted of adults of both sexes.

It was considered necessary to re-examine some patients due to considerably poorer results postoperatively compared with the preoperative investigation (cf. Results). Then, the tests of Claeson-Dahl, a verbal learning test ad modum Luria, and Cronholm-Molander, a test of visual memory function, were performed (8,31) in order to eliminate learning bias, which would be an obvious risk, if reusing the original test battery.

The criteria for reinvestigation were: Seven words or less postoperatively in the memory part of the Luria test or a post- to preoperative deficit of more than 2 words in this test (2 SD) (consensus of the Swedish National Board of Health); further, 26 points or less in the copy part of the Complex Figure test postoperatively, or 17 points or less in the memory part of the same test (32), or a post- to preoperative deficit of 3.5 or 5.5 points or more (1 SD), respectively, in either part of the Complex Figure test (own safety limits). Thus, a preoperative result just below the cut-off limit did not automatically qualify for re-examination. The learning part of the Luria test was not used for screening due to lack of documented cut-off limits.

Statistical analyses

All demographic, pharmacological and surgical variables in the groups were compared by the unpaired, two-sided t-test, Fisher's exact two-sided test or the Chi-square test, as considered appropriate. The coefficients of variation of individual mean isoflurane concentrations and mean infusion doses of propofol were calculated and compared.

A Pearson's product moment coefficient of correlation was calculated between the individual mean isoflurane concentrations and the CSF-AK activities, and the corresponding coefficient was calculated for the individual mean doses of propofol and the CSF-AK values. A coefficient of correlation, $r > 0.50$ was considered significant, giving $P < 0.05$ when $n=15$. The isoflurane and propofol data were also correlated to the outcome from psychometry by Kendall's rank correlation test.

The average CSF-AK results in the two hypnotic groups were compared by the unpaired, two-sided t-test. Fisher's exact two-sided test was used to evaluate the distribution of pathologic and non-pathologic results in the two groups.

The outcomes in the psychometric tests were compared by a paired, two-sided t-test, comparing pre- and postoperative test results. An unpaired two-sided t-test was used to compare the pre- and post-operative results within the groups. Fisher's exact two-sided test was used to evaluate the distribution of pathologic and non-pathologic results. The 5% significance level was chosen in all items.

Some subgroup analyses were considered necessary to undertake (cf. Results). In the case of subgroups consisting of less than ten patients the comparisons were made by the two-sided Mann-Whitney U-test, otherwise the unpaired, two-sided t-test was used. To evaluate differences in distributions Fisher's exact two-sided test or the Chi-square test was used (four-field and six-field tables, respectively).

Spreadware™ Statistics Menu, Stats 3 (Spreadware, USA) was combined with Microsoft™ Excel, version 5.0 (Microsoft Corporation, USA) for the statistical handling.

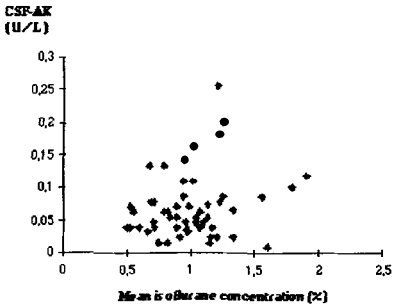
RESULTS

Three patients were excluded from the CSF-AK part of the study, one due to soft tissue swelling requiring semi-acute reintubation and two due to unwillingness to complete the study. Of the remaining 29 patients, 14 were in Group I and 15 in Group P. There were no differences between the groups regarding demographic or surgical variables, neither were there any differences in the administration of opioids. The group mean isoflurane concentration was 1.04% (SD 0.15) and the group mean propofol dose was 0.19 mg/kg/min (SD 0.03). The coefficients of variation of those mean values did not differ. Normoventilation and normal saturation were achieved in all instances, as well as the target level of anaesthesia. In eleven patients a decrease in MAP <50 mmHg made it necessary to infuse phenylephrine. None of the patients were given nitro-glycerine or metoprolol. The average blood loss for all patients was 267 mL (95% CI=164-371).

CSF-AK activity

A non-significant correlation coefficient, r, of 0.27 (P=0.36) was found between end-tidal isoflurane concentrations and CSF-AK values [Figure 1], and the corresponding r-value for propofol/CSF-AK was 0.34 (P=0.21). The mean CSF-AK activity did not differ significantly between groups I and P, nor did the percentage of pathological CSF-AK results (>0.040 U/L), which was 79% in Group I and 60% in Group P [Table 1].

Figure 1



Legend to Figure 1
Non-linear relationship between the CSF-AK values and individual mean isoflurane concentrations in 53 patients subjected to orthognathic surgery and anaesthetised with isoflurane, nitrous oxide and opioids. (r=0.20, n.s.). Data were pooled from the present study and Ref. 16 (the studies were comparable in regards of anaesthesia and orthognathic surgery, as well as the method to measure end-tidal concentration of isoflurane). The two tails may suggest occurrence of two patient populations.

Table 1. The distribution of non-pathological and pathological CSF-AK results in the hypnotic groups and their mean CSF-AK values

	Group I (n=14)	Group P (n=15)	
CSF-AK <0.040 (U/L)	3	6	n.s.
CSF-AK >0.040 (U/L)	11	9	
Mean CSF-AK (U/L)	0.065 [0.039]	0.051 [0.029]	n.s.

Note: CSF-AK = the activity of adenylate kinase in cerebrospinal fluid, mean [and SD].
Normal CSF-AK value is <0.040 U/L.

Post-hoc subgroup analyses - CSF-AK activity

Thirteen of the patients were constantly hypotensive in the current study (MAP 50-65 mmHg). They did not differ statistically significantly in CSF-AK values or in neuropsychological performance from nine constantly normotensive (MAP >65 mmHg) patients, or from eight patients who were fluctuating in blood pressure (not in Table). However, the median CSF-AK activity was 40% higher (0.067 U/L) in 5 patients in Group I, whom were given phenylephrine, than it was in the other 9 patients in Group I (0.048 U/L), or in the remaining 24 patients in the entire study (0.048 U/L). Two patients, expressing the overall highest CSF-AK values in the study, constituted the difference (P=0.05).

Psychometry

Two of the three patients excluded from the CSF-AK analysis were excluded from this part of the study, one due to the mentioned surgical complication and one due to unwillingness to complete the study. The former of the two patients performed poorly in several of the postoperative tests, compared with his preoperative test results, and would have been included in the follow-up study if he had complied. The preoperative test results revealed that the patients did not represent the normal population [Table 2]. Eighteen of 30 patients investigated performed below the cut-off level of a normal population in any of the tests. Some patients performed below cut-off limits in more than one of the tests. The results were evenly distributed between the hypnotic groups. The individual postoperative test results are presented in Table 2. Overall, the results from the Luria memory test decreased between the pre- and postoperative testing-sessions (P=0.01). The results from the Taylor-Rey-Osterreith Complex Figure test (copying) differed significantly between pre- and postoperative testing (P=0.04). However, in this case the test results were improved postoperatively, which is expected due to the fact that the patients were familiar with the test procedure (9,30). There were no significant differences concerning the other test variables over time, neither in the whole material, nor between the two groups. Individual results of interest: Ten patients, five from each hypnotic group, fulfilled the criteria for re-examination. They were all invited to

Table 2. Outcome of pre- and postoperative neuropsychological performances, using tests measuring different aspects of memory function, learning and attention.

No.	Luria learn.		Luria mem.		CF copy		CF mem.		WAIS	
	pre	post	pre	post	pre	post	pre	post	pre	post
	≤6 pts		≥8 words		≥27 pts		≥18 pts		≥5 pts	
1	3	5	10	9	29.0	30.0	26.5	26.5	6	7
2	7	>10	9	8	29.0	32.0	24.5	20.0	6	8
3	10	4	10	8	23.0	28.0	21.0	24.5	7	7
4	5	4	10	10	28.0	**26.0**	22.0	22.5	7	7
5	6	7	10	9	32.0	30.0	13.0	16.5	5	7
6	6	**>10**	8	**7**	26.0	27.0	14.5	15.0	6	7
7	5	6	8	9	27.0	26.0	24.0	**17.0**	7	7
8	6	5	10	9	20.5	28.0	18.5	19.0	8	8
9	9	2	10	10	29.5	27.0	18.5	24.0	6	6
10	10	>10	10	**4**	26.0	27.5	10.0	17.0	6	5
11	5	5	8	**7**	26.5	33.0	24.0	30.5	6	6
12	3	3	9	10	28.0	31.0	23.0	23.0	8	6
13	5	8	9	9	30.0	32.0	20.0	17.0	7	8
14	3	3	10	9	31.0	33.0	24.5	23.0	4	4
15	5	5	8	9	31.0	31.0	19.5	20.0	6	6
16	4	3	10	9	28.0	29.0	20.0	17.0	7	7
17	8	>10	9	**5**	21.5	28.5	9.5	15.0	6	6
18	10	8	9	**7**	21.5	29.0	5.5	6.5	4	5
19	6	5	10	8	30.0	32.0	31.0	29.0	6	5
20	5	4	10	8	28.0	28.0	15.5	21.0	8	8
21	5	5	10	10	25.0	24.0	21.0	23.5	5	6
22	4	5	10	9	29.0	**25.0**	18.0	**12.5**	7	7
23	6	6	8	8	30.0	28.0	13.5	**6.0**	8	5
24	6	6	10	8	21.0	22.0	15.5	16.0	5	6
25	5	3	10	9	25.0	30.0	20.5	18.0	7	6
26	5	3	8	9	31.0	31.0	21.5	20.5	5	6
27	4	6	9	8	32.0	31.0	20.5	25.0	6	5
28	5	5	10	10	26.0	28.0	27.0	**16.0**	5	5
29	2	3	8	9	33.0	31.0	22.0	19.5	5	5
30	3	3	9	10	30.0	29.0	15.0	17.5	7	7

Note: The limit of acceptance of each test is indicated in the heading. CF test = Taylor-Rey-Osterreith Complex Figure test.
Patients 1-15 = Group I, 16-30 = Group P. **Bold figures** = indication for post-study re-examination

a re-examination and were offered economic compensation for participation. Two patients from Group I and three from Group P accepted the invitation. One of the patients experienced surgery in-between the first postoperative tests and the reinvestigation. The results are summarised in Table 3, including self-reported information from a structured interview performed by the psychologist. Three patients showed test results indicating irreversible changes in memory function.

Table 3. Results of reinvestigation 12-30 months postoperatively in five patients, who failed in one or more of the first 4-8 weeks postoperative tests

Group	Sex	Age	10 words learning	10 words memory	Immediate memory	Memory after 45 min	Self reported symptoms
		years	≤6 repetitions	≥8 words	≥22 points	≥19 points	
I	f	71	**>10**	**6**	30	30	*
I	f	49	5	8	28	30	None
P	m	44	**>10**	**4**	**18**	23	None
P	m	45	4	10	24	20	None
P	m	25	**10**	9	22	22	None;‡

Note: The limit of acceptance of each test is indicated in the heading. Failed results are in **bold** figures.
* = Major difficulties to find words in discussions, needs to circumscribe; Some words, technical terms and expressions previously recognised are not familiar or easily recognised any longer.
‡ = Experienced several minor orthognathic surgical procedures between the present study and the re-investigation, one of them in general anaesthesia .

Post hoc subgroup analysis - Psychometry

The ten patients, who deteriorated in the postoperative psychometric tests (Subgroup D), were analysed statistically to look for any possible common properties, compared with the other 20 patients who did not pass any cut-off level (Subgroup N). Subgroup D differed significantly in several respects from subgroup N. They were heavier in weight, they were anaesthetised for a longer time, and they were given *less* of both fentanyl and alfentanil per kg per hour. They were also given *less* isoflurane or propofol, but, these differences were not statistically significant, P=0.11 and 0.06, respectively [Table 4]. Their blood loss was larger, in total and in rate of bleeding, though, in the latter aspect the difference was not significant (P=0.14). The distributions of gender, phenylephrine administration and surgical procedures were all uneven between subgroups, but none to statistical significance [Table 4]. Subgroup D did not differ in CSF-AK activity from Subgroup N [Table 5].

Table 4. Demograpic, pharmacologic and surgical characteristics in patients who deteriorated in neuropsychological tests postoperatively (Subgroup D) and patients who did not deteriorate (Subgroup N)

	Subgroup D (n=10)	Subgroup N (n=20)	Intergroup comparison
Assignation:			
isoflurane	5	10	
propofol	5	10	n.s.
***Gender:* Males**	7	9	
Females	3	11	n.s.
Age (years)	37.5 [16.8]	34.7 [14.0]	n.s.
Height (cm)	176.5 [12.0]	171.2 [7.5]	n.s.
Weight (kg)	80.9 [10.1]	68.9 [12.6]	$P<0.05$
Dur. of anaesth. (min)	234.3 [89.8]	177.0 [55.5]	$P<0.05$
Median dose iso			
(ET%)	0.96 (0.07) (n=5)	1.07 (0.14) (n=10)	n.s. ($P=0.11$)
pro (mg/kg/min)	0.18 (0.01) (n=5)	0.21 (0.02) (n=10)	n.s. ($P=0.06$)
fentanyl (µg/kg/h)	2.3 [0.7]	3.4 [0.7]	$P<0.05$
alfentanil (µg/kg/h)	7.7 [4.1]	13.7 [6.8]	$P<0.05$
Phenylephrine: No	5	14	n.s.
Yes	5	6	
Dur. of surgery (min)	207.7 [90.9]	155.5 [54.0]	n.s.
Blood loss, total (mL)	431.0 [402.6]	195.0 [157.6]	$P<0.05$
rate (mL/min)	1.9 [1.6]	1.3 [0.9]	n.s.
Localisation of surgery:			
Maxilla	5	16	
Mandible	2	2	n.s.
Both jaws	3	2	

Note to Table 3: Data are means [and SD] or median values (and inter quartile range) were applicable. The number of patients is given for group assignation, gender and localisation of surgery.

Table 5. *The distribution of non-pathological and pathological* CSF-AK results in patients who deteriorated in neuropsychological tests post-operatively (Subgroup D) and patients who did not deteriorate (Sub-group N) and their mean CSF-AK values

	Group D (n=10)	Group N (n=19)	
CSF-AK < 0.040 (U/L)	3	6	n.s.
CSF-AK > 0.040 (U/L)	7	13	
Mean CSF-AK (U/L)	0.057 [0.033]	0.058 [0.036]	n.s.

Note to Table 5: 19 patients in Group N, one patient who fulfilled psychometry refused lumbar puncture.
CSF-AK = the activity of adenylate kinase in cerebrospinal fluid, mean [and SD]. Normal CSF-AK values should be <0.040 U/L.

DISCUSSION

Psychometry

The main finding in the present study was that one-third of the patients deteriorated significantly in the post-operative neuropsychological tests, performed 4-8 weeks postoperatively, compared with their preoperative results. The mental sequel seemed to be irreversible for three of five patients re-tested 12-30 months later.

Healthy subjects who undergo verbal and figurative memory tests are not expected to perform differently between these two modalities (24). This strengthens the notion that the patients were not normally distributed regarding the psychometric variables measured in the present study. Non-impaired subjects were reported to achieve equivalent scores on the copy part of the Rey-Osterreith and the Taylor Complex Figure Tests in a test-retest experiment (10). However, the scores on the Taylor figure were significantly better on both immediate and delayed recall. It is difficult to interpret this result, since the order of the tests was not counter-balanced - the Rey-Osterreith figure was always administered first. In another study, in which the procedures were counter-balanced, a mixed group of neuropsychologically impaired adults performed equally between the two figures in both the copy and the memory part (22). When the performance of the Rey-Osterreith and the Taylor Complex Figures were compared in healthy subjects, using a counter-balanced protocol, it was found that the two different figures were compatible on copy, but not on recall (48). Thus, the results indicated that the Taylor figure was easier to remember. It was suggested though, that the subjects probably would anticipate the new figure when introduced during re-test, thus adopting a different type of encoding strategy than used in the original test phase. The subject probably shifted from an incidental to an intentional learning strategy.

Although, the findings in the above mentioned studies are not altogether conclusive, we however suggest that the deterioration in some patients in the Rey-Osterreith figure test in the present study reflected a true deterioration of one aspect of memory function. The translation of the present results into the everyday situation might be illustrated by quoting the hired psychologist who evaluated the Complex Figure tests. "People working with uncomplicated routine work might not recognise any disturbances, or just slight ones, but people studying at university will have problems to such an extent that they will perceive it" (Psychologist Inger Hagberg, Gothenburg). When Gruvstad et al, in the early 60's, discovered mental disturbances, persisting a year after hypotensive anaesthesia with trichlorethylene, pethidine and trimethaphan, his conclusion was "that the impairment has no practical effect on the subject's working capacity, adjustment to society or subjective well-being" (20). The attitude has changed since then, neither the speciality of anaesthesia, the authorities, nor the patients may accept sequel such as those we have found. It will be of pivotal importance to analyse the mechanisms behind the adverse effects. What is the impact of arterial hypotension, the anaesthetic drugs or the orthognathic surgery? Is it possible to identify risk factors?

For hypothesis generation Subgroups D and N were compared statistically in a number of properties [Table 4]. The risk of creating a type-I error by multiple statistical testing should be considered, however, in this

context, aiming at hypothesis generation, the effect of a type-II error would be of greater importance. A Bonferoni correction of *P*-values was undertaken for formal reasons. Then, one difference still was statistically different, the difference in fentanyl administration.

The patients

The patients in Subgroup D were significantly heavier in weight. This was most probably due to an over-representation of males, which did not reach statistical significance [Table 4]. The "mean" deteriorated patient was a 38 year old male, weighing 81 kg, operated on for almost 3½ hours, with 430 mL blood loss, and whom was given phenylephrine due to hypotension. The "mean" patient who did not deteriorate was a 35 year old female, weighing 69 kg, operated on for 2½ hours, with 195 mL blood loss, and whom was not given phenylephrine.

Some of the tendencies discussed above might be of major importance as risk factors, only possible to reveal in a larger study. The longer duration of surgery and larger loss of blood might be indicators of a more pronounced surgical trauma (c.f. down). The way in which surgical trauma can be harmful is at present not known. If male sex or heavy weight would be related to surgical problems or increased cerebral vulnerability is uncertain.

CSF-AK results

No significant statistical relationship was found between the end-tidal isoflurane concentrations and the CSF-AK values in the present study. However, the design of the study made this interpretation invalid, since the range of mean end-tidal isoflurane concentrations was narrow, compared with a previous study (16). Especially, the number of patients exposed to high concentrations was reduced when EEG/EMG response rather than the hemodynamic response directed anaesthesia. Recently, a dose-dependent increase of glutamate was measured in plasma during both isoflurane and propofol anaesthesia (43). Such an increase, which was highest during isoflurane anaesthesia, would increase the risk of oedema formation, an initial sign of toxicity, and potentially elevate CSF-taurine (43). This report may support our previous finding.

Arterial hypotension

In a previous study, arterial hypotension seemed to be without significance, regarding CSF-AK activity (16). Concerning psychometry, four patients out of 17 in the cited study deteriorated significantly in a limited test-battery. All four belonged to the hypotensive group, while none of the normotensive controls deteriorated. However, that distribution did not significantly differ from the null hypothesis. We know from case reports, that induced hypotension may be potentially dangerous, although it is proposed to be safe with modern techniques, both in general aspects and in terms of mental function (47,49). Experimentally, a case of global hypoxia was revealed by positron emission tomography during isoflurane-induced hypotension in a rhesus monkey (17). However, the process of hypoxia started already in a normotensive state in that animal, making it difficult to link hypoxia to hypotension. This animal, in which the isoflurane concentration was rapidly increased in contrast to other experiments, was later excluded from the study (15).

The role of arterial hypotension seemed to be minimal in the present study, despite the fact that in Subgroup D there was a slight overrepresentation of patients given phenylephrine. Neither was a direct effect of

phenylephrine likely, since phenylephrine is supposed not to pass the intact blood-brain-barrier to a considerable degree (12).

The anaesthetic drugs

There was, not unexpectedly, a discrepancy between the results from psychometry and the CSF-AK analyses. An explanation has been suggested (16). Briefly, we measured separate parts of a complex phenomenon with different methods. Still, in open-heart surgery, resulting in multi-focal brain infarctions, a statistical correlation was found between results of CSF-AK and psychometry. In the present study deterioration was associated with significantly lower doses of opioids and, not quite significant, lower doses of the hypnotic agents. It might be inferred from this post-hoc finding that the higher doses of the anaesthetic agents in Subgroup N had a protective effect. Besides conflicting information from the cerebral-protection-field, whether anaesthetic drugs have protective properties or not in ischemic situations (11,21,29,40,46), it is not obvious that this kind of discussion may be applicable to the present issue, in which the mechanism of injury is unclear.

On the contrary, it might be interpreted that the patients who deteriorated were more sensitive to the drugs, since they needed less of the drugs to reach the defined anaesthetic depth. This sensitivity may be combined with neuronal vulnerability. Differences do exist in the sensitivity to anaesthetic drugs in different populations of the same species in experimental studies (35,41). It is doubtful, but not without realism, whether this is true for humans, and whether vulnerability is related to increased sensitivity to anaesthetic drugs. The involvement of e.g. the $GABA_A$ receptor, which affects chloride channels, makes the question of different anaesthetic sensitivity interesting (41), as do the theories of the action of anaesthetic agents on neuronal membranes, implicating destabilisation from the solvent effect of volatile anaesthetics (6). Two populations of patients might be identified in this study and a previous one [Figure 1] (16). Leaving speculations, the role of the anaesthetic drugs was obscure. Undoubtedly, no effects of the drugs should be present 4-8 weeks postoperatively (4,9,30).

Equal anaesthetic depth in the hypnotic groups

The hypnotic groups were most probably comparable concerning the depth of anaesthesia. The EEG-ZCF and FEMG responses were equal in the groups, as well as the doses of opioids. Especially FEMG has been shown to be as reliable as mid-latency auditory evoked potentials to predict patient movement during anaesthesia (52). Consequently, the patients who deteriorated, receiving less drugs, were not lighter in anaesthetic depth, but more sensitive. Otherwise, light anaesthesia could have been an explanation for the increased duration of surgery and increased blood loss.

The orthognathic surgery

Vibrations, transmitted from the oscillating saw to the brain, have been suggested as an alternative explanation for the neuronal enzyme leakage detected (16). This suggestion was purely a theoretical one without support in the literature. Now, surgery will be taken into closer consideration.

If vibrations are of interest as a mechanism of injury, then maxillary surgery should possibly be worse, since the maxilla is closer and more fixed to the skull base and the brain than the mandible. The temporo-mandibular joint, with its disk, ought to damp the vibrations during mandibular procedures. However, maxillary surgery

was underrepresented in Subgroup D [Table 4]. On the other hand, in the low number of mandibular procedures sawing took up a greater part of surgery, since this bone is thicker than the maxilla. No strong conclusion can be drawn from this analysis.

There were other reasons for directing our interest to surgery. The patients in subgroup D were anaesthetised and operated on for a longer time than in Subgroup N. Intuitively, it is tempting to suggest that time might have impact on the results, whatever the mechanism of injury. For obvious reasons the duration of surgery was significantly longer in the combined procedures compared with surgery on one jaw only. The difference in duration of surgery between Subgroups D and N was in part explained by relatively more combined procedures in Subgroup D and fewer maxillary procedures [Table 4]. The difference in duration between Subgroups D and N was significant, if excluding the few mandibular procedures (not in Table).

Blood loss was larger in Subgroup D [Table 4]. As expected, single jaw procedures were associated with significantly less blood loss than combined procedures (not in Table). Since maxillary procedures were relatively few in Subgroup D, the difference in blood loss might be explained by this. However, the blood loss of the five patients with maxillary surgery in Subgroup D was larger than that of the 16 maxillary procedures in Subgroup N, supporting a true difference in blood loss. The median rate of bleeding was larger, as well as the duration of surgery in Subgroup D patients exposed to maxillary surgery. None of these differences were statistically significant, but the same proportions were found in the combined procedures, and taken together there was a statistically significantly larger blood loss in Subgroup D.

Differences in peroperative blood pressure could not explain the marked difference in blood loss between Subgroups D and N. There was an even distribution of hypotensive and normotensive patients in Subgroups D and N (not in Table).

The larger blood loss in Subgroup D ought to be an indicator of difficult surgery, secondary to the longer duration of surgery, at least in the case of maxillary and combined surgery. In all, in Subgroup D a more pronounced surgical trauma might be at hand. Although the blood loss in Subgroup D was more pronounced, it should not be a critical factor in itself, since it was fairly modest, 104-536 mL (95% CI), and no red blood cells were transfused. The blood loss was comparable with the findings in a previous study, and seemed to be low in comparison with some other studies (2,5,19,23).

Concluding remarks

The results from psychometry were remarkable. Some patients seemed to have developed irreversible functional impairment. We have no evident explanation for this. Several points of interest have arisen, especially surgical and individual factors, including the possible occurrence of a selective cerebral vulnerability in some patients. The role of the anaesthetic drugs was obscure, while arterial hypotension seemed not to be causal.

There is an obvious need for studies to confirm or reject the present findings, to evaluate the balance between benefits and risks of orthognathic surgery, and to investigate the outcome in other types of surgery with a comparable level of anaesthesia.

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REFERENCES

1. Adams JH, Brierly JB, Connor RCR, Treip CS. The effects of systemic hypotension upon the human brain. Clinical and neuropathological observations in 11 cases. Brain 1966; 89: 235-268.
2. Blau WS, Kafer ER, Anderson JA. Esmolol is more effective than sodium nitroprusside in reducing blood loss during orthognathic surgery. Anesth Analg 1992; 75: 172-178.
3. Brierly JB, Prior PF, Calverley J, Jackson SJ, Brown AW. The pathogenesis of ischaemic neuronal damage along the cerebral arterial boundary zones in papio anubis. Brain 1980; 103: 929-965.
4. Campbell DNC, Lim M, Kerr Muir M, O'Sullivan G, Falcon M, Fison P, Woods R. A prospective randomised study of local versus general anaesthesia for cataract surgery. Anaesthesia 1993; 48: 422-428.
5. Chan W, Smith DE, Ware WH. Effects of hypotensive anesthesia in anterior maxillary osteotomy. J Oral Surg 1980; 38: 504-508.
6. Chiou J-S, Tatara T, Sawamura S, Kaminoh Y, Kamaya H, Shibata A, Ueda I. The α-helix to β-sheet transition in poly(L-lysine):effects of anesthetics and high pressure. Biochim Biophys Acta 1992; 1119: 211-217.
7. Christensen A-L. Luria's neuropsychological investigation, 2nd ed. Copenhagen: Munksgaard, 1979.
8. Claeson LE, Esbjörnson E, Carlé BM, Wahlbin M. Cleason-Dahl inlärningstest för kliniskt bruk. Stochholm: Psykologförlaget AB, 1986.
9. Davison LA, Steinhelber JC, Eger II EI, Stevens WC. Psychological effects of halothane and isoflurane anesthesia. Anesthesiology 1975; 43: 313-324.
10. Delaney RC, Prevey ML, Cramer J, Mattson RH. Test retest comparability and control subject data for the PASAT REY-AVLT and Rey-Osterreith/Taylor figures [abstract]. J Clin Experiment Neuropsychol 1988; 10: 44
11. Drummond JC. Brain protection during anesthesia. A reader's guide [editorial]. Anesthesiology 1993; 79: 877-880.
12. Drummond J C, Shapiro H M. Cerebral physiology. In: Anesthesia (ed. Miller RD), pp 621-658. Churchill Livingstone Inc., New York, Edinburgh, London, Melbourne, Tokyo, 1990.
13. Edmonds HL Jr., Paloheimo M. Computerized monitoring of EMG and EEG during anesthesia: An evaluation of the anesthesia and brain activity brain monitor (ABM). Int J Clin Monit Comp 1985; 1: 201-210.
14. Enlund M, Ahlstedt B, Revenäs B, Krekmanov L, Ronquist G. Adverse effects on the brain in connection with isoflurane-induced hypotensive anaesthesia. Acta Anaesthesiol Scand 1989; 33: 413-415.
15. Enlund M, Andersson J, Hartvig P, Valtysson J, Wiklund L. Cerebral normoxia in the rhesus monkey during isoflurane- or propofol-induced hypotension and hypocapnia, despite disparate blood-flow patterns. A positron emission tomography study. Acta Anaesthesiol Scand 1997; 41: 1002-1010.
16. Enlund M, Mentell O, Flenninger A, Horneman G, Ronquist G. Occurrence of adenylate kinase in cerebrospinal fluid after isoflurane anaesthesia. Upsala J Med Sci 1996; 101: 97-112.

17. Enlund M, Wiklund L, Hartvig P, Andersson J, Lilja A, Långström B. Cerebral oxygenation during isoflurane- or propofol induced hypotension in the rhesus monkey. Global ischemia revealed by positron emission tomography [abstract]. Anesth Analg 1994; 78 (Suppl): S103.
18. Frithz G, Ronquist G, Hugosson R. Perspectives of adenylate kinase activity and glutathione concentration in cerebrospinal fluid of patients with ischemic and neoplastic brain lesions. Eur Neurol 1982; 21: 41-47.
19. Fromme GA, MacKenzie RA, Gould AB, Lund BA, Offord KP. Controlled hypotension for orthognathic surgery. Anesth Analg 1986; 65: 683-686.
20. Gruvstad M, Kebbon L, Ax:son Löf B. Changes in mental functions after induced hypotension. Acta Psych Scand 1962; 37: suppl 163.
21. Kochs E, Hoffman WE, Werner C, Thomas C, Albrecht RF, Schulte am Esch J. The effects of propofol on brain electrical activity, neurologic outcome, and neuronal damage following incomplete ischemia in rats. Anesthesiology 1992; 76: 245-252.
22. Kuehn SM, Snow WG. Are Rey and Taylor figures equivalent? A pilot study. Arch Clin Neuropsychol 1992; 7: 445-448.
23. Lessard MR, Trépanier CA, Baribault J-P, Brochu JG, Brousseau CA, Coté JJ, Denault PH. Isoflurane-induced hypotension in orthognathic surgery. Anesth Analg 1989; 69: 379-383.
24. Majdan A, Sziklas V, Jones-Gotman M. Performance of healthy subjects and patients with resection from the anterior temporal lobe on matched tests of verbal and visuoperceptual learning. J Clin Experiment Neuropsychol 1996; 18: 416-430.
25. Mentell O, Revenäs B, Jonsson L. A new hybrid anaesthetic circuit for a low-flow rebreading technique. Acta Anaesthesiol Scand 1994; 38: 840-844.
26. Miller ED Jr. Deliberate hypotension. In: Anesthesia (ed. Miller RD), pp 1347-1367. Churchill Livingstone, New York, Edinburgh, London, Melbourne, Tokyo, 1990.
27. Milner B. Psychological aspects of focal epilepsy and its neurosurgical management. In: Advances in Neurology (Vol 8) (eds. Purpura DP, Penry JK, Walter RD), pp 299-321. Raven Press, New York, 1975.
28. Milner B. Clues to the cerebral organization of memory. In: Cerebral correlates of conscious experience. INSERM symposium No 6 (eds. Buser P A, Rougene Buser A), pp 139-153. Elsevier/ North Holland Biomedical Press, Amsterdam, 1978.
29. Murphy PG, Myers DS, Davies MJ, Webster NR, Jones JG. The antioxidant potential of propofol. Br J Anaesth 1992; 68: 613-618.
30. Nielson WR, Gelb AW, Casey JE, Penny FJ, Merchant RN, Manninen PH. Long-term cognitive and social sequelae of general versus regional anesthesia during arthroplasty in the elderly. Anesthesiology 1990; 73: 1103-1109.
31. Nordgren J. Kliniska normer till Cronholm-Molanders minnesprov. Psykologiförlaget, Stockholm, 1978.
32. Osterreith PA. Le test de copie d'une figure complexe. Arch de Psychol 1944; 30: 206-356.
33. Paloheimo M, Edmonds HL Jr., Wirtavuori K, Tammisto T. Assessment of anaesthetic adequacy with upper facial and abdominal wall EMG. Eur J Anaesthesiol 1989; 6: 111-119.
34. Pasch T, Huk W. Cerebral complications following induced hypotension. Eur J Anaesthesiol 1986; 3: 299-312.
35. Quinlan JJ, Jin K, Gallaher EJ, McCrae AF, Firestone LL. Halothane sensitivity in replicate mouse lines selected for diazepam sensitivity or resistance. Anesth Analg 1994; 79: 927-932.
36. Rey A. L'examen psychologique dans le cas d'encepalopatie traumatique. Arch de Psychol 1941; 28: 286-340.
37. Richards CD. Cellular mechanisms of anaesthesia. Current Opinion in Anaesthesiology 1993; 6: 616-619.
38. Ronquist G, Callerud T, Niklasson F, Friman G. Studies of biochemical markers in cerebrospinal fluid in patients with meningoencephalitis. Infect Immun 1985; 48: 729-734.
39. Ronquist G, Terent A. Cerebrospinal fluid markers of disturbed brain cell metabolism. Prog Neurobiol 1982; 18: 167-180.

40. Sano T, Drummond JC, Piyush MP, Grafe MR, Watson JC, Cole DJ. A comparison of the cerebral protective effects of isoflurane and mild hypothermia in a model of incomplete forebrain ischemia in the rat. Anesthesiology 1992; 76: 221-228.
41. Simpson VJ, Blednov Y. Propofol produces differences in behaviour but not chloride channel function between selected lines of mice. Anesth Analg 1996; 82: 327-331.
42. Spreen O, Strauss E. A compendium of neuropsychological tests. Oxford University Press, New York, 1991.
43. Stover JF, Vrana S, Schäfer M, Kempski OS. Isoflurane increases glutamate and taurine in csf: evidence of cell swelling? [abstract]. Acta Anaesthesiol Scand 1996; 40 (Suppl 109): 214.
44. Taylor LB. Localization of cerebral lesions by psychological testing. Clin Neurosurg 1969; 16: 267-287.
45. Taylor LB. Psychological assessment of neurosurgical patients. In: Functional neurosurgery (eds. Rasmussen T, Mariano R), pp 165-180. Raven Press, New York, 1979.
46. Todd MM, Warner DS. A comfortable hypothesis reevaluated. Anesthesiology 1992; 76: 161-164.
47. Toivonen J, Kuikka P, Kaukinen S.: Effects of deliberate hypotension induced by labetalol with isoflurane on neuropsychological function. Acta Anaesthesiol Scand 1993; 37: 7-11.
48. Tombaugh TN, Hubley AM. Four studies comparing the Rey-Osterreith and Taylor Complex figures. J Clin Experiment Neuropsychol 1991; 13: 587-599.
49. Townes BD, Dikmen SS, Bledsoe SW, Hornbein TF, Martin DC, Janesheski JA. Neuropsychological changes in a young, healthy population after controlled anesthesia. Anesth Analg 1986; 65: 955-959.
50. Vreca I, Derganc M, Grosek S. Adenylate kinase in the cerebrospinal fluid of hypoxic newborns. Clin Biochem 1989; 22: 135-139.
51. Wechsler D. WAIS-R, Wechsler Adult Intelligence Scale - Revised. The Psychological Corporation Harcourt Brace Jovanovich Inc, San Antonio, Texas, 1981.
52. Yli-Hankala A, Edmonds Jr. HL, Heine MF, Strickland Jr. T, Tsueda K. Auditory steady-state response, upper facial EMG, EEG and heart rate as predictors of movement during isoflurane-nitrous oxide anaesthesia. Br J Anaesth 1994; 73: 174-179.
53. Åberg T, Ronquist G, Tydén H, Brunnkvist S, Hultman J, Bergström K, Lilja A. Adverse effects on the brain in cardiac operations as assessed by biochemical, psychometric, and radiologic methods. J Thorac Cardiovasc Surg 1984; 87: 99-105.
54. Åberg T, Tydén H, Ronquist G, Åhlund P, Bergström K. Release of adenylate kinase into cerebrospinal fluid during open-heart surgery and its relation to postoperative intellectual function. Lancet 1982; i: 1139-1142.

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