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Intracranial Volume–Pressure Relationship following Thiopental or Etomidate

*Alan A. Artru, M.D.**

A series of infusions of mock cerebrospinal fluid (CSF) was used to determine intracranial volume–pressure relationships in 18 anesthetized dogs. Measures of intracranial volume–pressure relationships included 1) CSF pressure prior to volume infusion (P_0), 2) peak CSF pressure (P_p) caused by volume injection, 3) intracranial compliance (C, calculated as the ratio of change of intracranial volume [ΔV] to change of CSF pressure [ΔP]), 4) the volume–pressure response (VPR, a measure of elastance, calculated as the ratio of ΔP to ΔV), 5) the pressure volume index (PVI, calculated as the ratio of ΔV to log P_p/P_0), and 6) estimated intracranial compliance (C_e, calculated from PVI as 0.4343 PVI/P_0). Six of the 18 dogs (time controls) were studied during halothane (0.4%, end expired) and nitrous oxide (66%) in oxygen, six dogs were studied prior to and following each of two doses of thiopental (approximate cumulative doses were 10.5 and 25.5 mg/kg), and six dogs were studied prior to and following each of two doses of etomidate (approximate cumulative doses were 1.52 and 3.70 mg/kg). In the time controls P_0, P_p, C, VPR, PVI, and C_e were steady throughout the experimental period. Thiopental decreased P_0 (by 2–3 ± 1 cmH_2O) and P_p (by 2–4 ± 2 cmH_2O), increased C_e (by 0.02–0.03 ± 0.01 ml/cmH_2O), and did not change C, VPR, or PVI. Etomidate decreased P_0 (by 3–4 ± 1 cmH_2O) and P_p (by 4–6 ± 2 cmH_2O), increased C_e (by 0.03–0.04 ± 0.01 ml/cmH_2O) and did not change C, VPR, or PVI. It is concluded that under conditions of "normal" P_0 and no intracranial pathology, repeated testing of intracranial volume–pressure relationship is possible as long as the exact volume of CSF infused for each test is then withdrawn prior to subsequent infusions, and at least 15 min are allowed for reequilibration between repeated tests. At the doses used here, thiopental and etomidate produce comparable decreases of P_0 and P_p, increases of C_e (a measure strongly influenced by P_0), and no significant change in the intracranial volume–pressure relationship as indicated by C, VPR, or PVI. (Key words: Anesthetics, intravenous: etomidate; thiopental. Brain: intracranial pressure; volume–pressure relationship. Cerebrospinal fluid: pressure; volume–pressure relationship. Hypnotics: etomidate; thiopental.)

THIOPENTAL AND ETOMIDATE are recommended for induction of anesthesia for patients with increased intracranial pressure (ICP) resulting from cerebral edema or space-occupying lesions.[1,2] These recommendations are based on reports that both thiopental and etomidate reduce increased ICP so that ICP becomes closer to normal. Although it is useful to know that thiopental and etomidate reduce increased ICP, those data alone provide little information about the effects of thiopental and etomidate on intracranial volume–pressure relationships. The effects of these treatments on the volume–pressure relationship are relevant to clinical practice because improvement of the intracranial volume–pressure relationship presumably improves survival and neurologic outcome by reducing the liklihood for recurrence of increased ICP.[3,4] This decreases the risk for cerebral ischemia, minimizes the pressure applied to brain tissue, and reduces the mechanical damage caused by shift or displacement of brain tissue within the intracranial space.

Three well-known methods for assessing the intracranial volume–pressure relationship are intracranial compliance (C), the volume–pressure response (VPR, a measure of intracranial elastance),[5–9] and the pressure volume index (PVI, a measure relating change of intracranial volume [ΔV] and log ICP).[10–12] The present study was designed to determine the effects of thiopental and etomidate on cerebrospinal fluid (CSF) pressure, these three measures of the intracranial volume–pressure relationship, and other characteristics of the CSF pressure response following volume injection into the CSF space. It was speculated that the effects of small doses of thiopental on the intracranial volume–pressure relationship may be less favorable than those of small doses of etomidate. This speculation was based on a previous report that resistance to reabsorption of CSF was greater with small doses of thiopental than with small doses of etomidate.[13]

Methods

Animal Preparation

This study was approved by the Animal Care Committee of the University of Washington. Eighteen unmedicated mongrel dogs (weights 14–22 kg) were studied. Anesthesia was induced with halothane (~2.5% inspired) and nitrous oxide (N_2O, 66%, inspired) in oxygen. The trachea was intubated, expired CO_2 was continuously monitored (Beckman Medical Gas Analyzer, Model LB2, Beckman Instruments, Inc., Fullerton, California), and ventilation was regulated by a servocontroller to maintain expired CO_2 at normocapnia. The right femoral artery was cannulated to permit arterial blood sampling for blood gas analysis and to permit continuous monitoring of systemic arterial pressure and heart rate. Mean arterial pressure (MAP) was determined by electronic integration. A urinary catheter was inserted, the right femoral vein was cannulated for saline and drug administration and temperature was monitored by a nasopharyngeal thermistor

* Professor of Anesthesiology.

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Address reprint requests to Dr. Artru: Department of Anesthesiology, RN-10, University of Washington School of Medicine, Seattle, Washington 98195.

probe. Intravenous infusion of vecuronium 2–4 mg/h maintained muscle relaxation.

A burr hole was placed over the left hemisphere and a catheter was directed into the underlying lateral ventricle for measurement of ventricular CSF pressure (cmH_2O). The posterior neck muscles were surgically separated to expose the atlanto-occipital membrane and a catheter was directed into the cisterna magna. A T-connector was attached to the catheter to permit measurement of cisternal CSF pressure along with infusion and withdrawal of fluid at the cisterna magna. A 0.3 ml sample of CSF was obtained from the cisternal cannula for measurement of osmolality using a Wescor Model 5100 B Vapor Pressor Osmometer (Wescor, Inc., Logan, Utah). Mock CSF of matching osmolality was prepared by mixing standard solutions of osmolality 290, 300, or 310 mOsm/kg.[14] A syringe containing mock CSF was attached to the infusion/withdrawal limb of the cisternal T-connector. Wound edges were infiltrated with bupivacaine (0.5%), and the concentration of halothane was decreased to 0.4% (end-expired value determined intermittently by gas chromatography, N_2O unchanged). Details of this animal preparation have been previously reported.[13]

Experimental Period

The experimental period began once systemic variables had stabilized (at least 25 min after decreasing the concentration of halothane). The experimental period consisted of six infusions of mock CSF into the cisterna magna. Infusions 1, 3, and 5 were 0.5 ml given over 2.5 s, while infusions 2, 4, and 6 were 1.0 ml given over 5.0 s (timed infusion *via* syringe). Each infusion caused an abrupt increase of ventricular and cisternal CSF pressure, followed by a slower, biphasic return of CSF pressure toward pre-infusion values (fig. 1). The CSF pressure response to each volume infusion was permitted to continue for 3 min. At 3 min after volume infusion, 0.5 or 1.0 ml was withdrawn from the cisterna magna to restore CSF volume to its pre-infusion value. After each withdrawal of CSF volume, at least 15 min was allowed for CSF pressure to return to its pre-infusion value. Succeeding CSF volume infusions were not made until CSF pressure was within 1 cmH_2O of the pre-infusion value. Two infusion volumes (0.5 and 1.0 ml) were used because it was not known whether the standard infusion volume of 1.0 ml initially described for patients[5–9] might be too large for dogs. Thus, at each condition the first infusion volume was 0.5 ml (infusions 1, 3, and 5). If the increase of CSF pressure did not exceed 55 cmH_2O, 0.5 ml was withdrawn from the CSF space and 1.0 ml was injected while still at the same experimental condition (infusions 2, 4, and 6).

CSF pressure responses to volume infusion were recorded on a chart recorded for analysis after the conclusion of the experiment. The values determined from each CSF pressure response were CSF pressure prior to volume infusion (P_0), peak CSF pressure following volume infusion (P_p), the three aforementioned, calculated measures of the intracranial volume–pressure relationship, and other characteristics of the CSF pressure response to volume infusion.

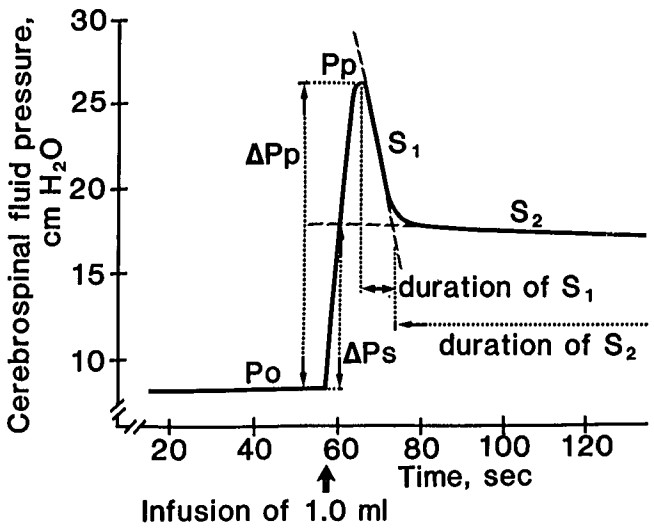

FIG. 1. The CSF pressure response to infusion of 1.0 ml is shown for one of the time control dogs. Duration of S_1 is the time from P_p to the intersection of S_1 with S_2, and duration of S_2 is the time from intersection of S_1 with S_2 until return to P_0.

The three aforementioned, calculated measures of the intracranial volume–pressure relationship were C, VPR, and PVI. C was calculated as the ratio of ΔV to change of CSF pressure (ΔP). C values were expressed as ml/cmH_2O. VPR was calculated as the ratio of ΔP to ΔV.[5–9] VPR values were expressed as cmH_2O/ml. PVI was calculated as $\Delta V/[\log P_p/P_0]$.[10–12] Calculated PVI values were expressed as ml. Marmarou *et al.*, who described PVI, also described an estimate of C (C_e) based on the values obtained with PVI.[10–12] Utilizing their equation, C_e was calculated as $[0.4343\ (PVI)]/P_0$. Calculated C_e values were expressed as ml/cmH_2O.

Other characteristics of the CSF pressure response to volume infusion were the first phase slope of decrease of CSF pressure from P_p (S_1), the second phase slope of decrease (S_2), and the CSF pressure change equalling the difference between P_0 and the CSF pressure at which extrapolation of S_2 intersected the slope of CSF pressure increase from P_0 (ΔP_s). S_1 and S_2 were expressed as cmH_2O/min and ΔP_s was expressed as cmH_2O/ml. Another characteristic of the CSF pressure response, the slope of the CSF pressure increase caused by volume infusion, did not vary between animals and conditions and presumably reflected chiefly the rate and volume of in-

fusion. Consequently, S_1, S_2, and ΔP_s were determined for each volume infusion and the slope of the CSF pressure increase was not determined. The duration of S_1 was determined as the time from P_p to the intersection of S_1 with S_2. The duration of S_2 was calculated as the time from the intersection of S_1 with S_2 to the intersection of extrapolated S_2 with P_0.

In each of six dogs (time controls), six infusions of mock CSF were made during anesthesia with halothane 0.4% and N_2O 66% in oxygen. In six other dogs (thiopental group), CSF infusions 1 and 2 were made prior to administration of thiopental, CSF infusions 3 and 4 were made after the first dose of thiopental (6.0 mg/kg given intravenously over 5–10 min followed by infusion at 6.0 $mg \cdot kg^{-1} \cdot h^{-1}$), and CSF infusions 5 and 6 were made after the second dose of thiopental (another 6.0 mg/kg followed by 12.0 $mg \cdot kg^{-1} \cdot h^{-1}$).[13] In the final six dogs (etomidate group), CSF infusions 1 and 2 were made prior to administration of etomidate, CSF infusions 3 and 4 were made after the first dose of etomidate (0.86 mg/kg followed by 0.86 $mg \cdot kg^{-1} \cdot h^{-1}$), and CSF infusions 5 and 6 were made after the second dose of etomidate (another 0.86 mg/kg followed by 1.72 $mg \cdot kg^{-1} \cdot h^{-1}$).[13] In the thiopental and etomidate groups halothane (0.4%) and N_2O (66%) in oxygen were continued during administration of both doses of thiopental and etomidate.

Statistical Analysis

Statistical comparisons within groups were made using repeated-measures analysis of variance, and comparisons between groups were made using one-way analysis of variance.[15] Where the calculated F value exceeded the critical value for the 0.05 probability level, the Student-Newman-Keuls' test was used to determine which differences were significant at $P < 0.05$.[16] Values are tabulated as mean ± SD.

Results

P_0, P_p, C, VPR, PVI, C_e, S_1, S_2, ΔP_s, and systemic values (with the exception of heart rate) were not significantly different between the three groups during infusions 1 and 2 (*i.e.*, at the time when all dogs were receiving only halothane [0.4%] and nitrous oxide [66%] in oxygen; tables 1–4). P_p did not exceed 55 cmH_2O with any of the infusions of 0.5 ml mock CSF; thus, all dogs were tested with both 0.5 ml and 1.0 ml infusions of mock CSF at all experimental conditions. C, VPR, PVI, C_e, S_2, and ΔP_2 based on 0.5 ml infusions were not significantly different from values based on 1.0 ml infusions. Values for P_p and S_1 were increased with 1.0 ml infusions compared with 0.5 ml infusions. The duration of S_1 (11 ± 1 s) was substantially shorter than the duration of S_2 (8 ± 4 min).

Time Controls

Repeated infusion and withdrawal of mock CSF at the cisterna magna did not change P_0 over the duration of the study. In addition, P_p, C, VPR, PVI, C_e, S_1, S_2, and ΔP_s were not significantly different when compared among the three 0.5 ml infusions (infusions 1, 3, and 5) or among the three 1.0 ml infusions (infusions 2, 4, and 6).

Thiopental Group

The first dose of thiopental decreased P_0 (by 2 ± 1 cmH_2O) and P_p (by 4 ± 2 cmH_2O) and increased C_e (by

TABLE 1. Responses to Volume Injection in Time Controls (mean ± SD; n = 6)

	1 0.5 ml	2 1.0 ml	3 0.5 ml	4 1.0 ml	5 0.5 ml	6 1.0 ml
Pre-infusion cerebrospinal fluid pressure (cmH_2O)	7 ± 2	—	7 ± 2	—	7 ± 2	—
Peak cerebrospinal fluid pressure (cmH_2O)	24 ± 6	35 ± 5*	24 ± 6	35 ± 5*	24 ± 7	36 ± 5*
Intracranial compliance (ml/cmH_2O)	0.03 ± 0.01	0.04 ± 0.01	0.03 ± 0.01	0.04 ± 0.01	0.03 ± 0.01	0.03 ± 0.01
Volume–pressure response, (cmH_2O/ml)	32 ± 6	27 ± 5	33 ± 6	27 ± 5	33 ± 7	28 ± 5
Pressure volume index (ml)	1.5 ± 0.2	1.7 ± 0.2	1.5 ± 0.2	1.7 ± 0.2	1.5 ± 0.2	1.7 ± 0.2
Estimated intracranial compliance (ml/cmH_2O)†	0.09 ± 0.01	0.10 ± 0.01	0.09 ± 0.01	0.10 ± 0.01	0.09 ± 0.01	0.10 ± 0.01
S_1 (cmH_2O/min)	79 ± 19	109 ± 23*	74 ± 16	104 ± 23*	78 ± 18	108 ± 21*
S_2 (cmH_2O/min)	0.5 ± 0.2	0.6 ± 0.2	0.5 ± 0.2	0.4 ± 0.2	0.4 ± 0.2	0.6 ± 0.2
ΔP_s (cmH_2O/ml)	9 ± 1	11 ± 2	9 ± 1	10 ± 2	8 ± 1	10 ± 2

Throughout the tables, numbers 1–6 refer to the infusion number, and 0.5 ml and 1.0 ml are infusion volumes.

* Significant difference compared with corresponding 0.5 ml value ($P < 0.05$).

† Based on pressure–volume index values.

TABLE 2. Responses to Volume Injection in the Thiopental Group (mean ± SD; n = 6)

	Prethiopental		Thiopental Dose 1		Thiopental Dose 2	
	1 0.5 ml	2 1.0 ml	3 0.5 ml	4 1.0 ml	5 0.5 ml	6 1.0 ml
Pre-infusion cerebrospinal fluid pressure (cmH_2O)	9 ± 2	—	7 ± 1*	—	6 ± 1*	—
Peak cerebrospinal fluid pressure (cmH_2O)	24 ± 5	34 ± 4‡	20 ± 5*	30 ± 3*‡	22 ± 5*	30 ± 4*‡
Intracranial compliance (ml/cmH_2O)	0.03 ± 0.01	0.04 ± 0.01	0.04 ± 0.01	0.04 ± 0.01	0.03 ± 0.01	0.04 ± 0.01
Volume–pressure response (cmH_2O/ml)	30 ± 5	25 ± 4	26 ± 5	23 ± 3	29 ± 5	24 ± 4
Pressure volume index (ml)	1.7 ± 0.3	1.9 ± 0.3	1.6 ± 0.3	1.7 ± 0.3	1.5 ± 0.3	1.6 ± 0.3
Estimated intracranial compliance (ml/cmH_2O)†	0.09 ± 0.01	0.10 ± 0.01	0.12 ± 0.02*	0.12 ± 0.02*	0.12 ± 0.02*	0.12 ± 0.02*
S_1 (cmH_2O/min)	74 ± 15	95 ± 17‡	77 ± 17	108 ± 19‡	78 ± 16	114 ± 23‡
S_2 (cmH_2O/min)	0.3 ± 0.1	0.5 ± 0.1	0.4 ± 0.1	0.5 ± 0.1	0.4 ± 0.1	0.5 ± 0.1
ΔP_s (cmH_2O/ml)	9 ± 1	11 ± 3	7 ± 1	10 ± 2	8 ± 1	9 ± 2

* Significant difference compared with corresponding prethiopental value ($P < 0.05$).

† Based on pressure–volume index values.

‡ Significant difference compared with corresponding 0.5 ml value ($P < 0.05$).

0.03 ± 0.01 ml/cmH_2O when the injection volume was 0.5 ml and by 0.02 ± 0.01 ml/cmH_2O when the injection volume was 1.0 ml) compared with prethiopental values. C, VPR, PVI, S_1, S_2, ΔP_s, and systemic values were not significantly different from prethiopental values.

The second dose of thiopental decreased P_0 (by 3 ± 1 cmH_2O) and P_p (by 2–4 ± 2 cmH_2O), and increased C_e (by 0.03 ± 0.01 ml/cmH_2O when the injection volume was 0.5 ml, and by 0.02 ± 0.01 ml/cmH_2O when the injection volume was 1.0 ml) compared with prethiopental values. P_0, P_p, and C_e were not different after the first dose of thiopental. C, VPR, PVI, S_1, S_2, ΔP_s, and systemic values were not significantly different from prethiopental values. With both thiopental doses P_p and S_1 were increased with 1.0 ml infusions compared with 0.5 ml infusions.

ETOMIDATE GROUP

The first dose of etomidate decreased P_0 (by 3 ± 1 cmH_2O) and P_p (by 4–6 ± 2 cmH_2O), and increased C_e (by 0.03 ± 0.01 ml/cmH_2O when the injection volume was 0.5 ml, and by 0.04 ± 0.01 ml/cmH_2O when the

TABLE 3. Responses to Volume Injection in the Etomidate Group (mean ± SD; n = 6)

	Pre-etomidate		Etomidate Dose 1		Etomidate Dose 2	
	1 0.5 ml	2 1.0 ml	3 0.5 ml	4 1.0 ml	5 0.5 ml	6 1.0 ml
Pre-infusion cerebrospinal fluid pressure (cmH_2O)	9 ± 1	—	6 ± 1*	—	5 ± 1*	—
Peak cerebrospinal fluid pressure (cmH_2O)	22 ± 3	33 ± 2‡	18 ± 4*	27 ± 2*‡	17 ± 2*	27 ± 2*‡
Intracranial compliance (ml/cmH_2O)	0.04 ± 0.01	0.04 ± 0.01	0.04 ± 0.01	0.05 ± 0.01	0.04 ± 0.01	0.05 ± 0.01
Volume–pressure response (cmH_2O/ml)	27 ± 3	24 ± 2	24 ± 4	21 ± 2	23 ± 2	22 ± 2
Pressure–volume index (ml)	1.7 ± 0.2	1.9 ± 0.2	1.5 ± 0.2	1.5 ± 0.2	1.5 ± 0.2	1.5 ± 0.2
Estimated intracranial compliance (ml/cmH_2O)†	0.09 ± 0.01	0.09 ± 0.01	0.12 ± 0.01*	0.13 ± 0.01*	0.13 ± 0.01*	0.13 ± 0.02*
S_1 (cmH_2O/min)	66 ± 11	89 ± 21‡	75 ± 18	96 ± 22‡	69 ± 12	102 ± 22‡
S_2 (cmH_2O/min)	0.4 ± 0.1	0.5 ± 0.1	0.4 ± 0.1	0.3 ± 0.1	0.3 ± 0.1	0.3 ± 0.1
ΔP_s (cmH_2O/ml)	10 ± 2	13 ± 2	7 ± 1*	10 ± 2	7 ± 1	10 ± 2‡

* Significant difference compared with corresponding pre-etomidate value ($P < 0.05$).

† Based on pressure–volume index values.

‡ Significant difference compared with corresponding 0.5 ml value ($P < 0.05$).

TABLE 4. Systemic Values during Infusions 1 and 2, prior to Administration of Thiopental or Etomidate (mean ± SD)

	Time Controls (n = 6)	Thiopental Group (n = 6)	Etomidate Group (n = 6)
Mean arterial blood pressure (mmHg)	97 ± 8	106 ± 6	104 ± 6
Heart rate (beats/min)	100 ± 5	108 ± 3*	92 ± 5*
Pa_{CO_2} (mmHg)	37 ± 1	35 ± 2	37 ± 1
*p*H	7.37 ± 0.01	7.37 ± 0.02	7.36 ± 0.02
Bicarbonate (mEq/l)	20.5 ± 0.6	19.9 ± 0.3	19.8 ± 0.3
Pa_{O_2} (mmHg)	169 ± 7	155 ± 7	165 ± 4
Hemoglobin (g/dl)	12.8 ± 0.9	13.8 ± 0.9	14.7 ± 0.6
Temperature, nasopharyngeal (° C)	37.3 ± 0.4	37.3 ± 0.4	37.0 ± 0.2

* Significant difference between thiopental and etomidate groups ($P < 0.05$).

injection volume was 1.0 ml) compared with preetomidate values. The magnitude of the changes in P_0, P_p, and C_e was not significantly different from that seen following the first dose of thiopental. In addition, heart rate decreased to 79 ± 5 beats/min following the first dose of etomidate. C, VPR, PVI, S_1, S_2, ΔP_s, and other systemic values were not significantly different from preetomidate values.

The second dose of etomidate decreased P_0 (by 4 ± 1 cmH_2O) and P_p (by 5–6 ± 2 cmH_2O), and increased C_e (by 0.04 ± 0.01 ml/cmH_2O) compared with preetomidate values. P_0, P_p, and C_e were not different than after the first dose of etomidate. The magnitude of the changes in P_0, P_p, and C_e were not significantly different from those seen following the second dose of thiopental. C, VPR, PVI, S_1, S_2, ΔP_s, and systemic values were not significantly different than after the first dose of etomidate. With both etomidate doses P_p and S_1 were increased with 1.0 ml infusions compared with 0.5 ml infusions.

Discussion

Time Controls

The results from the time controls indicate that mock CSF may be repeatedly infused and withdrawn at the cisterna magna without altering P_0 as long as the volume withdrawn matches the volume infused. Also, repeated trials of volume infusion (with subsequent withdrawal of an equivalent volume) does not alter P_p, calculated measures of intracranial volume–pressure relationship (C, VPR, and PVI) or characteristics of the CSF pressure response (S_1, S_2, and ΔP_s). Most of these values were not different when 0.5 ml was used as the volume of injection than when 1.0 ml was used as the volume of injection.

Two exceptions were P_p and S_1, where values increased when the injection volume was 1.0 ml. These findings demonstrate that initially the rate of return of CSF pressure toward pre-infusion values is more rapid when a higher P_p is achieved. The short duration of S_1 (11 ± 1 s) suggests that this measure represents accommodation to CSF volume increase by rapidly changing responses, such as translocation of CSF to immediately accessible areas and venous compression.[17] The longer duration of S_2 (8 ± 4 min) suggests that this measure represents accommodation to CSF volume increase by events that proceed more slowly, such as reabsorption of CSF and translocation of CSF to poorly accessable areas.[17]

Thiopental and Etomidate Groups

In the thiopental and etomidate groups, the decrease of CSF pressure observed with these drugs is consistent with previous reports of their effects on ICP.[1,2] In the present studies the findings that P_0 and P_p decreased with both doses of thiopental and etomidate, and that the decreases were not different with thiopental than with etomidate suggests no clear superiority of either drug at the doses used here. However, the findings that P_0 and P_p following thiopental were similar to that following etomidate does not rule out the possibility of intracranial differences between the two drugs. It was previously reported that ICP could be normal despite severe disturbance of the intracranial volume–pressure relationship, as with the presence of a sizable intracranial mass lesion.[18,19] Thus, CSF pressure may not be a useful measure to distinguish differences between thiopental and etomidate regarding their effects on intracranial volume–pressure relationships.

For that reason, calculated measures of the intracranial volume–pressure relationship (C, VPR, and PVI) were also employed in the present study. In both of the drug-treated groups no significant change in C, VPR, or PVI was seen following administration of thiopental or etomidate. These results indicate no improvement in the intracranial volume–pressure relationship and argue against the idea that measurement of CSF pressure would have failed to detect an intracranial difference between the two drugs if it had been the only measure employed in this study.

A calculated measure that did change following thiopental and etomidate was C_e. C_e expresses the relationship between ΔV and ΔP as a quotient of P_0. Treatment-induced improvements in the relationship between ΔV and ΔP are therefore magnified if the treatment also decreases P_0. As a result, statistically insignificant changes in the relationship between ΔV and ΔP may achieve statistical significance when calculated in terms of C_e if the treatment also decreases P_0.

It should be kept in mind that the present studies were performed in dogs with "normal" CSF pressure and no

intracranial pathology. Under these conditions both doses of thiopental and etomidate produced comparable decrease of P_0 and P_p, and improvement in C_e. It is not known whether thiopental and etomidate would decrease P_0 and P_p, and improve C_e under conditions of elevated P_0 or in the presence of an intracranial mass, and if so, whether the effects of the two drugs still would be comparable. Also, under the present conditions thiopental and etomidate did not improve C, VPR, or PVI. C, VPR, and PVI not only distinguish between "normal" and impaired intracranial volume–pressure relationship, but also indicate changes in intracranial volume–pressure relationship when that relationship is compromised. Thus, it is possible that under conditions of elevated P_0 or an intracranial space-occupying lesion, thiopental and etomidate may improve C, VPR, or PVI and, if so, that there may be differences between the two drugs.

Prior to beginning this study it was speculated that because resistance to reabsorption of CSF previously was reported to be greater with small doses of thiopental than with small doses of etomidate, the volume–pressure relationship may be less favorable with thiopental.[13] The present results do not support that speculation. The failure to observe differences between thiopental and etomidate for C, VPR, PVI, C_e, S_1, and ΔP_s likely relates to the speed of the initial intracranial volume response to infusion of mock CSF. This initial response was so rapid ($S_1 = 11 \pm 1$ s) that only a small volume of CSF could have been reabsorbed during that time. The larger contributions of CSF translocation and venous compression to the initial response would obscure any drug-induced differences in volume of CSF reabsorption.[17] In contrast, the duration of S_2 was found to be of sufficient length (8 ± 4 min) that differences between thiopental and etomidate for resistance to reabsorption of CSF might be expected to produce differences of S_2. However, this potential difference likely was obscured by the large variability of S_2 values, where the SD ranged from 20–50% of the mean.

Based on the results of this study, the following conclusions are made: 1) repeated volume–pressure testing is possible providing the volume withdrawn exactly matches the volume infused at each trial and at least 15 min is allowed for reequilibration between trials, 2) an injection volume of either 0.5 ml or 1.0 ml is suitable for dogs of this size, 3) small doses of thiopental and etomidate produce similar reductions in P_0 and P_p, and improvement in C_e (a measure strongly influenced by P_0) but no significant change in the intracranial volume–pressure relationship as indicated by C, VPR, or PVI in dogs with "normal" CSF pressure and no intracranial pathology, and 4) because the equation for C_e magnifies the effect of P_0, in the present study C_e was more a descriptor of P_0 than of C.

References

1. Campkin TV, Turner JM: Intracranial effects of anaesthetic agents, Neurosurgical Anaesthesia and Intensive Care. Edited by Campkin TV, Turner JM. London, Butterworths, 1986, pp 48–72
2. Samuels SI: Anesthesia for supratentorial tumor, Anesthesia and Neurosurgery. Edited by Cottrell JE, Turndorf H. St. Louis, CV Mosby, 1986, pp 114–130
3. Miller JD, Becker DP, Ward JD, Sullivan HG, Adams WE, Rosner MJ: Significance of intracranial hypertension in severe head injury. J Neurosurg 47:503–516, 1977
4. Langfitt TW, Gennarelli TA: Can the outcome from head injury be improved? J Neurosurg 56:19–25, 1982
5. Miller JD, Pickard JD: Intracranial volume–pressure studies in patients with head injury. Injury 5:265–269, 1974
6. Miller JD, Garibi J: Intracranial volume–pressure relationships during continuous monitoring of ventricular fluid pressure, Intracranial Pressure. Edited by Brock M, Deitz H. Berlin, Springer-Verlag, 1972, pp 270–274
7. Miller JD, Leech PJ, Pickard JD: Volume–pressure response in various experiments and clinical conditions, Intracranial Pressure. Edited by Lundberg N, Ponten U, Brock M. Berlin, Springer-Verlag, 1975, pp 97–100
8. Miller JD: Volume and pressure in the craniospinal axis, Clinical Neurosurgery, Vol. 22. Edited by Wilkins RH. Baltimore, Williams & Wilkins, 1975, pp 76–105
9. Miller JD: Intracranial pressure–volume relationships in pathological conditions. J Neurosurg Sci 20:203–209, 1976
10. Marmarou A, Shulman K, LaMorgese J: A compartmental analysis of compliance and outflow resistance and the effects of elevated blood pressure, Intracranial Pressure. Edited by Lundberg N, Ponten U, Brock M. Berlin, Springer-Verlag, 1975, pp 86–88
11. Marmarou A, Shulman K, LaMorgese J: Compartmental analysis of compliance and outflow resistance of the cerebrospinal fluid system. J Neurosurg 43:523–534, 1975
12. Marmarou A, Shapiro K, Shulman K: Isolating factors leading to sustained elevations of the ICP, Intracranial Pressure. Edited by Beks JWF, Bosch DA, Brock M. Berlin, Springer-Verlag, 1976, pp 33–35
13. Artru AA: Dose-related changes in the rate of cerebrospinal fluid formation and resistance to reabsorption of cerebrospinal fluid following administration of thiopental, midazolam and etomidate in dogs. ANESTHESIOLOGY 69:541–546, 1988
14. Davson H: Chemical composition and secretory nature of the fluids, Physiology of the Cerebrospinal Fluid. Edited by Davson H. London, Churchill, 1970, pp 33–54
15. Brunning JL, Kintz BL: Analysis of variance, Computational Handbook of Statistics. Edited by Brunning JL, Kintz BL. Glenview, IL, Scott, Foresman, 1977, pp 18–106
16. Steel RGD, Torrie JH: Analysis of variance: I. The one-way classification, Principles and Procedures of Statistics. Edited by Steel RGD, Torrie JH. New York, McGraw-Hill, 1960, pp 99–131
17. Bruce DA: Cerebrospinal fluid pressure dynamics and brain metabolism, Neurobiology of Cerebrospinal Fluid. Edited by Wood JH. New York, Plenum, 1980, pp 351–363
18. Sullivan HG, Miller JD, Becker DP, Flora RE, Allen RA: The physiological basis of ICP change with progressive epidural brain compression; an experimental evaluation in cats. J Neurosurg 47:532–550, 1977
19. Weaver DD, Winn AR, Jane JA: Differential intracranial pressure in patients with unilateral mass lesions. J Neurosurg 56:660–665, 1982