Experimental Correction of Hypercapnic Intracranial Hypertension

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It has long been known that a dilatation of vessels of the brain occurs during asphyxia. It is also well established that an increase in CO_2 concentration in the blood produces a vasodilation of the cerebral vessels [1, 2] and an increase in blood flow through the brain.[3, 4] However, it was not before 1930 that Wolff and Lennox [5] demonstrated the correlation between an increase in the CO_2 content of the blood and a rise in cerebrospinal fluid (CSF) pressure. Their findings were further substantiated by many workers who studied animals breathing high concentrations of CO_2.[6] Draper and Whitehead [7] amplifying an earlier observation by Volhard [8] produced in dogs hypercapnic acidosis by their technique of "diffusion respiration," (called by the present authors "apneic oxygenation"). They noted with Goldensohn [9] a marked and early increase in CSF pressure. Similar observations were made by Small *et al.*[10] who induced respiratory arrest with succinylcholine instead of the overdose of thiopental used by Draper and Whitehead. A rise in CSF pressure was noticeable after 90 seconds when Pa_{CO_2} had increased by about 8–10 mm. of mercury. After 2 minutes of "apneic oxygenation" the CSF pressure rose an average of 126 per cent. After 9 minutes and 24 seconds it reached an average peak of 375 mm. of water. They further demonstrated that the cardiovascular and respiratory effects of CO_2 are of little importance in producing changes in CSF pressure, suggesting that increased intracranial pressure could result from clinically undetected hypercapnia.

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The purpose of the present experiments was to compare the effects of an organic hydrogen ion acceptor of low toxicity, 2-amino-2-hydroxymethyl-1,3-propanediol or tris(hydroxymethyl)aminomethane (THAM) on intracranial hypertension of hypercapnic acidosis with the effects of other agents used to relieve elevated intracranial pressure.

Materials and Methods

Seventeen adult mongrel dogs weighing 12–16 kg. were used. Ten minutes after subcutaneous injection of atropine sulfate (0.3–0.4 mg.), the dogs were lightly anesthetized with 25 mg./kg. of thiopental given intravenously. Their tracheas were immediately intubated with a cuffed endotracheal tube maintained above the carina and no more barbiturate was administered. Lid areflexia was generally avoided. Respiratory paralysis was induced by 0.5 mg./kg. of succinylcholine administered intravenously and the animals' lungs were ventilated with 100 per cent oxygen by means of a pressure controlled mechanical ventilator. Paralysis was maintained by additional doses of succinylcholine (average total dose of 3 mg./kg.). The ventilator was driven at the rate of 16–18/minute with a ratio of inspiration to expiration of 1 : 2. The endotracheal tube was also connected through one arm of a three-way stopcock to a Benedict-Roth metabolism apparatus filled with oxygen. CSF pressure was measured via a 20-gauge Quincke-Babcock spinal needle inserted into the cisterna magna and connected by a polyethylene catheter to a P 23 BB Statham pressure transducer, and a Sanborn Twin-Viso recorder. Arterial blood pressure was recorded via a femoral artery polyethylene catheter and a P 23 AA Statham pressure transducer. Intravenous fluid was administered by a catheter introduced into the femoral vein. A

TABLE 1. Average Changes in Pressure and Acid-Base Balance in Cerebrospinal Fluid and Arterial Blood of Dogs after Two 30 Minute Periods of Apneic Oxygenation

	Pressure		pH		HCO_3^- mM./L.		P_{CO_2} mm. Hg		Urine Output ml.
	mm. Hg Blood	mm. H_2O C.S.F.	Arterial Blood	C.S.F.	Arterial Blood	C.S.F.	Arterial Blood	C.S.F.	
Control	117 (100–138)*	61 (40–100)	7.60 (7.55–7.64)	7.54 (7.48–7.59)	15.5 (13.1–22.1)	19.5 (12.9–24.1)	21.1 (14.1– 40.4)	31.3 (25.5– 47.7)	0
A.O.	122 (110–138)	147 (90–184)	6.87 (6.78–6.92)	6.93 (6.76–7.18)	26.3 (22.1–30.7)	19.9 (17.0–24.8)	157.0 (133.4–208.4)	117.4 (97.1–169.5)	4 (2– 10)
Control	123 (100–150)	12 (0– 30)	7.58 (7.55–7.63)	7.45 (7.31–7.58)	15.6 (14.0–20.0)	18.2 (15.6–20.4)	24.3 (15.7– 34.8)	33.4 (25.9– 34.4)	15 (6– 40)
A.O. +THAM	133 (105–156)	26 (0– 70)	7.50 (7.34–7.77)	7.34 (7.21–7.46)	38.1 (32.5–42.6)	17.4 (15.6–21.7)	58.6 (46.1– 77.7)	51.1 (43.2– 76.2)	209 (152–250)
Control	128 (90–150)	36 (25– 46)	7.60 (7.55–7.68)	7.51 (7.45–7.60)	14.2 (10.8–19.1)	20.6 (19.0–21.5)	15.1 (11.0– 22.3)	27.1 (20.6– 32.7)	0
A.O.	133 (120–150)	153 (70–206)	6.90 (6.86–6.94)	6.80 (6.73–6.89)	28.6 (24.4–31.6)	21.1 (19.5–24.1)	150.3 (110.7–168.1)	143.6 (131.8–158.9)	7 (4– 10)
Control	141 (110–170)	12 (0– 20)	7.60 (7.48–7.67)	7.35 (7.21–7.44)	17.1 (12.2–22.3)	17.3 (16.7–17.9)	19.0 (11.6– 30.6)	34.9 (26.4– 47.7)	15 (12– 18)
A.O. +THAM-Cl	131 (120–146)	102 (86–110)	7.00 (6.95–7.04)	6.89 (6.79–7.03)	28.3 (26.2–32.1)	19.8 (17.8–22.3)	116.7 (99.0–148.6)	110.3 (90.1–135.0)	180 (150–210)

* Range.
During the second period of A.O. the animals were treated as indicated. Each figure represents the average of 3–4 measurements. Trends reported in the average results (increase or decrease) were present in all individual experiments. C.S.F.: cerebrospinal fluid; A.O.: apneic oxygenation.

urinary catheter was inserted into the bladder which was emptied at the start of the first period of "apneic oxygenation" and urinary output was recorded throughout the experiment.

At regular intervals during each experiment, arterial blood and CSF samples were obtained simultaneously and anaerobically. The volume of CSF withdrawn at any one time was never more than 0.5 cc., and it was immediately replaced by the same amount of normal saline; if the CSF was bloody the experiment was discounted. Blood and CSF *p*H were determined with a model R Cambridge potentiometer and a Sanz micro glass electrode at 37.5° C. Plasma and CSF CO_2 content were determined on the Kopp-Natelson microgasometer.[11] CO_2 partial pressure and bicarbonate ion concentration were calculated with the Henderson-Hasselbalch equation. All analyses were performed in duplicate.

After one hour of denitrogenation the animal was submitted to two 30 minute periods of apneic oxygenation. Thirty minutes of mechanical ventilation separated the two periods of apneic oxygenation. It was established in three experiments that animals subjected to this procedure presented a similar rise in CSF pressure during both periods of apneic oxygenation. The compound to be tested was given during the second period of apneic oxygenation. Five series of experiments were performed. At 0.3 *M* solution of THAM * was given intravenously to the first group of dogs at the rate of 1 ml./kg./minute. The second group received the same amount of THAM titrated to *p*H 7.40 by the addition of 210 mEq/l. of hydrochloric acid. The third group was treated with 0.6 *M* D-mannitol administered intravenously at the rate of 1 ml./kg./minute. The osmolarity of this solution is similar to that of the titrated THAM. A similar amount of 0.3 *M* solution of urea was given to the fourth group. The fifth group of dogs was perfused with 30 per cent urea in 10 per cent invert sugar,† at the rate of 0.3 ml./kg./minute.

Results (Tables 1 and 2)

In all experiments there was a four to five-fold increase in CSF pressure after the first period of apneic oxygenation. Mean blood pressure rose or remained constant. Arterial blood and CSF *p*H fell below 7.0, while P_{CO_2} and HCO_3^- increased in both media. Urinary output was negligible.

In the animals treated with THAM, CSF pressure remained within normal limits, blood pressure did not change, and arterial blood

* Talatrol, Abbott Laboratories, North Chicago, Illinois.
† Urevert, Travenol Laboratories, Inc., Morton Grove, Illinois.

TABLE 2. Average Changes in Pressure and Acid-Base Balance in Cerebrospinal Fluid and Arterial Blood of Dogs after Two 30 Minute Periods of Apneic Oxygenation

	Pressure		pH		HCO_3^- m.M./L.		P_{CO_2} mm. Hg		Urine Output ml.
	mm. Hg Blood	mm. H_2O C.S.F.	Arterial Blood	C.S.F.	Arterial Blood	C.S.F.	Arterial Blood	C.S.F.	
Control	122 (104–144)*	44 (16– 70)	7.50 (7.40–7.62)	7.47 (7.38–7.54)	15.7 (11.9–17.4)	20.4 (17.7–22.8)	21.5 (11.8– 27.0)	29.9 (21.8– 35.3)	0
A.O.	150 (128–192)	277 (255–296)	6.84 (6.78–6.91)	6.87 (6.79–6.94)	21.7 (18.0–23.7)	21.4 (18.0–23.9)	132.5 (98.4–158.1)	165.6 (160.0–167.7)	5 (2– 10)
Control	128 (90–156)	30 (10– 40)	7.39 (7.29–7.44)	7.34 (7.29–7.38)	16.1 (13.9–17.7)	18.2 (17.2–19.7)	27.3 (20.9– 35.0)	35.6 (31.5– 43.2)	10 (5– 16)
A.O.+Mannitol	161 (124–188)	155 (116–188)	6.73 (6.59–6.83)	6.73 (6.57–6.85)	21.5 (20.4–23.7)	18.7 (16.8–20.6)	169.3 (141.7–225.6)	151.2 (121.7–199.8)	215 (150–280)
Control	165 (160–170)	63 (30– 95)	7.43 (7.41–7.44)	7.38 (7.35–7.44)	19.6 (17.6–20.6)	20.6 (20.4–20.7)	30.1 (26.5– 33.1)	36.9 (32.0– 39.4)	0
A.O.	180 (165–200)	190 (115–270)	6.81 (6.76–6.84)	6.76 (6.72–6.80)	29.3 (27.1–31.2)	21.1 (20.8–21.5)	188.2 (181.8–194.0)	159.2 (143.9–169.6)	11 (10– 14)
Control	180 (175–190)	70 (55– 95)	7.36 (7.22–7.45)	7.29 (7.18–7.36)	19.8 (17.6–22.3)	18.2 (16.8–19.6)	37.8 (26.2– 55.8)	41.3 (33.6– 56.0)	26 (20– 34)
A.O.+Urea	198 (170–225)	357 (300–400)	6.75 (6.66–6.85)	6.73 (6.65–6.81)	26.8 (26.2–27.4)	20.8 (19.5–22.5)	197.0 (161.7–242.9)	168.3 (129.1–198.2)	63 (40– 94)
Control	150 (145–155)	53 (40– 80)	7.39 (7.35–7.41)	7.34 (7.21–7.50)	14.9 (12.3–17.6)	18.8 (17.4–20.0)	25.3 (20.0– 31.4)	37.6 (27.2– 46.2)	0
A.O.	190 (150–210)	247 (175–320)	6.64 (6.54–6.73)	6.58 (6.32–6.74)	24.9 (22.2–26.4)	18.9 (17.0–21.8)	238.2 (204.3–268.7)	178.2 (148.6–220.0)	10 (8– 15)
Control	130 (120–140)	33 (15– 50)	7.40 (7.28–7.53)	7.22 (7.20–7.29)	13.3 (11.8–15.5)	16.0 (15.0–16.6)	21.9 (19.1– 25.4)	41.8 (33.1– 47.4)	13 (10– 16)
A.O.+Urea and invert sugar	207 (170–230)	100 (65–135)	6.64 (6.57–6.74)	6.74 (6.63–6.94)	26.4 (23.5–28.4)	21.0 (20.4–21.4)	250.3 (212.8–276.1)	172.7 (105.7–206.6)	72 (15–120)

* Range.

During the second period of A.O. the animals were treated as indicated. Each figure represents the average of 3–4 measurements. Trends reported in the average results (increase or decrease) were present in all individual experiments. C.S.F.: cerebrospinal fluid; A.O.: apneic oxygenation.

*p*H was maintained within ± 0.1 *p*H unit. A rise in P_{aCO_2} was limited by the increase in plasma HCO_3^-. In the CSF, *p*H fell by about 0.1 *p*H unit, bicarbonate fell slightly, and P_{CO_2} rose. A marked diuresis started 3 to 5 minutes after the onset of apnea and was maintained after restoration of mechanical ventilation and cessation of the infusion of THAM.

The animals treated with buffered THAM and those treated with mannitol presented similar, though not identical, pictures. There was a rise in CSF pressure which was less than in the first apneic control period. This increase in pressure, however, was not as great (102 instead of 155 mm. of mercury) in the dogs treated with titrated THAM, and acid-base relationships in blood and CSF were less altered. During the period of apnea urine output was marked in both series and similar to that of the animals treated with THAM at *p*H 10.2. The animals treated during apnea with a 0.3 *M* solution of urea had the highest CSF pressure. They also had hypertension, arrhythmias and hematuria. Urinary output was well below fluid input. The administration of urea-invert sugar was accompanied by a three-fold increase in CSF pressure instead of a five-fold one as in the control period. Diuresis was marked and comparable to that of the dogs treated with THAM or mannitol, urine output tending to match fluid input.

Discussion

The present series of experiments confirms the effectiveness of THAM in correcting the acute intracranial hypertension of hypercapnic acidosis.[12, 13] That this correction requires a normal blood *p*H is borne out by these observations. The administration of THAM titrated to *p*H 7.40 is accompanied by a rise in CSF pressure. This increase, however, is not as great as the increase with 0.6 *M* mannitol which completely lacks buffering activity and is accompanied by a greater degree of acidosis. However, the relationship between increase in CSF pressure and acid-base balance changes in blood and CSF cannot be closely analysed in the present experiments, where the samples of CSF were replaced by normal saline, thus altering the bicarbonate concentration and acid-base balance in this compartment. It can only be pointed out that, in the presence of minimal fluid load, a rise in CSF pressure is

accompanied by a fall in *p*H and an increase in P_{CO_2}, both in arterial blood and CSF. As reported previously, there is little correlation between arterial and CSF pressures.[10] It is apparent that THAM acts through both its osmotic and buffering properties, since a THAM solution titrated to *p*H 7.40 with HCl partially corrects the rise in CSF pressure during apenic oxygenation. When 0.6 *M* D-mannitol is administered in an amount which will produce a diuresis similar to that of titrated THAM, but not correct the acidosis at all, the rise in CSF pressure is more pronounced. A mixture of urea and dextrose reduces the intracranial pressure to a greater extent than THAM-chloride or mannitol. Two factors may be responsible for this: the much smaller fluid load (0.3 ml./kg./minute instead of 1 ml./kg./minute) and the marked increase in blood osmolality which accompanies the infusion of urea-invert sugar. Neither titrated THAM nor mannitol change blood osmolality to a similar extent and it is the difference in osmolality between blood and CSF induced by urea which appears to be responsible for the CSF pressure reduction.[14] Furthermore, such a correction is even better maintained in the absence of urinary excretion.[15] As THAM is a potent diuretic, it may have a limited effect on the relief of intracranial hypertension associated with brain compression. It is noteworthy that even a very hypertonic solution such as urea-invert sugar (5.3 molar, 18 times the osmolarity of the blood) did not completely correct the intracranial hypertension of hypercapnic acidosis, whereas an isosmolar solution of urea increased the hypertension and produced hematuria. This rise in intracranial pressure during urea-invert sugar infusion could not be accounted for by the fluid load. An expansion of extracellular space, as shown by Fishman,[16] is a contributing factor in the production of intracranial hypertension, but in this instance, after 20 minutes, urine output closely matched fluid input and fluid load was minimal. The partial correction of hypercapnic intracranial hypertension by agents which exert an osmotic activity could indicate that hypercapnic acidosis and its resulting cerebral vasodilation may also be accompanied by a transfer of water from vascular to cerebrospinal compartments, or possibly, from extracellular to intracellular spaces. This hypothesis, however, requires further experimental testing.

These series of experiments indicate that the intracranial hypertension of hypercapnic acidosis cannot be corrected by agents which only have osmotic properties. Such a correction requires the restoration of acid-base balance either by THAM administration or hyperventilation.[17]

Summary

Hypercapnic acidosis was produced in 17 dogs by maintaining them in apneic oxygenation for 30 minutes. There was a three to five-fold increase in cerebrospinal fluid (CSF) pressure, while arterial and CSF *p*H fell by 0.6 *p*H unit. During a second period of apneic oxygenation, one group of dogs received an infusion of 0.3 *M* tris(hydroxymethyl)aminomethane (THAM). CSF pressure did not change, marked diuresis was present, arterial and CSF *p*H remained within 0.1 *p*H unit of control while arterial and CSF P_{CO_2} rose respectively from 24 to 58 and 33 to 51 mm. of mercury. Two other groups of dogs were given 0.6 *M* mannitol or 0.3 *M* THAM titrated to *p*H 7.40 with HCl. In both instances diuresis was maintained and the increase in CSF pressure was half that of the control hypercapnic period, while blood and CSF *p*H and P_{CO_2} changes were the same. When 0.3 *M* urea was administered, the increase in CSF pressure was greater than in the control apneic period. Marked hematuria was present and blood pressure rose by an average of 30 mm. of mercury. When a 30 per cent solution of urea in 5 per cent dextrose (5.3 *M*) was administered CSF pressure rose from 33 to 100 mm. of water and blood pressure from 130 to 207 mm. of mercury *p*H and P_{CO_2} changes were similar to those recorded in the control apneic period. Marked diuresis was present. Intracranial hypertension of hypercapnic acidosis cannot be corrected by agents which have only osmotic properties. This correction requires a restoration of *p*H to normal which can be accomplished by hyperventilation or by THAM administration.

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CEREBROSPINAL FLUID The *p*H and P_{CO_2} were studied in arterial blood and cerebrospinal fluid in normal subjects and in patients with respiratory insufficiency. With hyperventilation the alkalosis that resulted was more severe in arterial blood than in spinal fluid. Inhalation of 5 per cent carbon dioxide decreased *p*H in arterial blood more than in spinal fluid. Respiratory insufficiency produced a difference between arterial blood and cerebrospinal-fluid *p*H that was greater than normal despite a P_{CO_2} difference that was less. (*Merwarth, C. R., and others: Acid-Base Relations Between Blood and Cerebrospinal Fluid in Normal Subjects and Patients with Respiratory Insufficiency, New Engl. J. Med. 265: 310 (Aug. 17) 1961.*)