

The Effects of Nitroglycerin on Cerebrospinal Fluid Pressure in Awake and Anesthetized Humans

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The effects of nitroglycerin on cerebrospinal fluid pressure (CSFP) and arterial blood pressure were studied in 56 patients with normal CSFP. Thirty-two patients were studied while awake, and 24 while anesthetized with thiamylal, nitrous oxide and oxygen. Nitroglycerin administered as an iv bolus produced marked increases in CSFP and decreases in arterial pressure in all patients studied. Maximal changes in CSFP seen at 1-2 min following nitroglycerin, 4 $\mu\text{g}/\text{kg}$ and 8 $\mu\text{g}/\text{kg}$, were 190 ± 8.3 (mean \pm SE) and 286 ± 53.6 per cent of control, respectively. The increases in CSFP were transient and return to control values occurred within 2-3 min after the injection. The increase in CSFP and the decrease in arterial blood pressure occurred virtually simultaneously. There were no statistically significant differences in the changes in CSFP and arterial pressure between awake and anesthetized subjects. These data suggest that in patients with decreased intracranial compliance, nitroglycerin may cause undesirable increases in CSFP; further this effect may not be blocked by prior administration of drugs such as thiamylal. (Key words: Anesthetic techniques: induced hypotension; nitroglycerin. Blood pressure: hypotension. Cerebrospinal fluid: pressure.)

VASODILATING AGENTS such as sodium nitroprusside,¹ trimethaphan,¹ and hydralazine² can increase intracranial pressure (ICP) in patients with intracranial mass lesions. Although it had been suggested as a drug of choice for inducing hypotension during neurosurgical procedures,³ nitroglycerin was recently reported to cause a marked increase in intracranial pressure in the management of a patient who had intracranial hypertension.⁴ In cats anesthetized with halothane, nitroglycerin produced an increase in intracranial pressure as well as a decrease in arterial blood pressure; larger increases in intracranial pressure were always associated with larger decreases in blood pressure.⁵ As far as we know, there have been no reports in normal awake or anesthetized humans regarding the effects of nitroglycerin on intracranial pressure. We therefore measured changes in cerebrospinal fluid pressure after a bolus injection of nitroglycerin in humans who were awake and during anesthesia.

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Materials and Methods

Fifty-six adult patients (36 males, 20 females), who were scheduled to have spinal anesthesia for their surgical procedure, were studied while awake or during thiamylal, nitrous oxide and oxygen anesthesia. The protocol was approved by the Institutional Human Studies Committee and informed consent was obtained from each patient. All patients were free from cardiopulmonary or neurological disorders. Pre-medication with hydroxyzine, 1.0-1.4 mg/kg, and atropine, 0.4-0.5 mg, was administered by im injection 1 hour before arrival in the operating room. An intravenous catheter was placed for infusion of lactated Ringer's solution and an arterial catheter was inserted into the radial artery for measurement of arterial blood pressure and for sampling of arterial blood for blood gas analyses. Following sterile preparation and draping of the lumbar region with the patient in the lateral position, a 22-gauge spinal needle was inserted through the L4-L5 intervertebral space. Upon demonstration of the free flow of clear cerebrospinal fluid, the needle was connected with a low-compliance catheter to an appropriate transducer for continuous measuring of CSF pressure. The inside of the catheter was filled with sterile normal saline solution so as not to remove CSF, and care was taken to avoid introduction of air bubbles into the line. The zero reference point for the CSFP was at the midline of the vertebral column. Thereafter the patient was maintained in the lateral position with the head and vertebrae in a straight line. ECG, arterial blood pressure, and CSF pressure were continuously recorded.

Nitroglycerin,[§] either 4 $\mu\text{g}/\text{kg}$ or 8 $\mu\text{g}/\text{kg}$, was injected intravenously as a bolus in 32 awake patients and 24 anesthetized patients. In the latter group, general anesthesia was induced by thiamylal, 4.0 mg/kg, nitrous oxide, 4 l/min, and oxygen, 2 l/min, via a semiclosed carbon dioxide absorption system. Nitroglycerin was administered 3-5 min after the induction of anesthesia. Mean arterial pressure was calculated as diastolic blood pressure plus one-third the pulse pressure and mean cerebrospinal fluid pressure was calculated as diastolic CSF pressure

§ Nippon Kayaku Co., 0.5 mg/ml in 10 ml ampule.

TABLE 1. Characteristics of Patients and Blood Gas Values before and after Nitroglycerin in Four Groups of Patients

	Awake		Anesthesia	
	4 $\mu\text{g}/\text{kg}$	8 $\mu\text{g}/\text{kg}$	4 $\mu\text{g}/\text{kg}$	8 $\mu\text{g}/\text{kg}$
Number of patients	17	15	12	12
Age (years)	46 \pm 4	41 \pm 4	46 \pm 6	42 \pm 5
Body weight (kg)	58.8 \pm 1.8	60.2 \pm 2.7	57.0 \pm 2.4	59.9 \pm 3.2
pH				
before	7.36 \pm 0.01	7.37 \pm 0.01	7.38 \pm 0.02	7.37 \pm 0.01
after	7.36 \pm 0.01	7.38 \pm 0.01	7.40 \pm 0.01	7.35 \pm 0.01
P _a CO ₂ (torr)				
before	38 \pm 1	37 \pm 1	38 \pm 1	40 \pm 2
after	38 \pm 1	38 \pm 1	38 \pm 2	41 \pm 1
P _a O ₂ (torr)				
before	86 \pm 3	86 \pm 2	167 \pm 12	163 \pm 16
after	85 \pm 3	82 \pm 3	167 \pm 16	149 \pm 15
BE (mEq/l)				
before	-0.2 \pm 0.1	-0.2 \pm 0.1	-0.2 \pm 0.1	-0.1 \pm 0.1
after	-0.3 \pm 0.1	-0.2 \pm 0.1	-0.1 \pm 0.1	-0.3 \pm 0.1

Values are means \pm SEM.

plus one-half the intraspinal pulse pressure.¹ All data within groups were compared using Student's *t* test for paired data. Data between groups were compared by analysis of variance and Student's *t* test for unpaired data. *P* values of 0.05 or less were regarded as statistically significance. Data were expressed as means \pm SEM.

Results

There were no significant differences between patient groups in the mean values for age and body weight and the control values for blood gases, arterial pressure, heart rate and CSFP (tables 1 and 2). Nitroglycerin, 4 $\mu\text{g}/\text{kg}$ and 8 $\mu\text{g}/\text{kg}$, produced decreases in arterial blood pressure and marked increases in CSFP in every patient studied (table 2). Heart rate also increased significantly (table 2). Each decrease in blood pressure and increase in CSFP occurred

within 30 s after the injection, and then gradually returned to control values in 3–5 min (fig. 1). The maximal changes in CSFP in awake subjects following nitroglycerin, 4 $\mu\text{g}/\text{kg}$ and 8 $\mu\text{g}/\text{kg}$, were to 187 \pm 9 and 293 \pm 71 per cent of control, respectively.

When thiamylal was given to 24 patients, both CSFP and blood pressure initially decreased, the former from 9.3 \pm 1.1 torr to 5.3 \pm 1.0 torr. At the time of administration of nitroglycerin, CSFP had returned to the awake value while blood pressure had not (table 2). Nitroglycerin produced almost the same magnitude of increases in CSFP and decreases in arterial blood pressure in the anesthetized subjects as in the awake subjects (table 2). The mean increases in CSFP were to 193 \pm 14 per cent of control with 4 $\mu\text{g}/\text{kg}$ nitroglycerin and to 280 \pm 74 per cent of control with 8 $\mu\text{g}/\text{kg}$.

The increase in CSFP was always associated with a predominant increase in intraspinal pulse pressure

TABLE 2. Mean \pm SEM Values of Mean Arterial Blood Pressure (MAP), Heart Rate, CSFP, and Cerebral Perfusion Pressure at Control and Maximal Changes Following Nitroglycerin, 4 $\mu\text{g}/\text{kg}$ or 8 $\mu\text{g}/\text{kg}$, iv

	MAP (torr)		Heart rate (beat/min)		Mean CSFP (torr)		Cerebral Perfusion Pressure (torr)	
	Control	Maximal Change*	Control	Maximal Change*	Control	Maximal Change*	Control	Maximal Change
Awake subjects								
4 $\mu\text{g}/\text{kg}$ (n = 17)	107 \pm 5	86 \pm 4	75 \pm 3	93 \pm 4	8.1 \pm 1.2	14.8 \pm 2.2	99.4 \pm 4.8	71.5 \pm 5.1*
8 $\mu\text{g}/\text{kg}$ (n = 15)	105 \pm 4	85 \pm 3	80 \pm 4	97 \pm 4	8.9 \pm 1.4	19.3 \pm 2.0	96.0 \pm 3.8	65.6 \pm 3.9*
Anesthetized subjects								
4 $\mu\text{g}/\text{kg}$ (n = 12)	92 \pm 5	79 \pm 6	80 \pm 3	94 \pm 4	8.6 \pm 1.5	15.8 \pm 2.5	83.5 \pm 4.7	69.2 \pm 6.1†
8 $\mu\text{g}/\text{kg}$ (n = 12)	94 \pm 5	78 \pm 4	80 \pm 4	91 \pm 5	9.1 \pm 1.4	20.0 \pm 1.7	84.6 \pm 4.5	57.6 \pm 3.2*

* *P* < 0.01 vs. control.

† *P* < 0.05 vs. control.

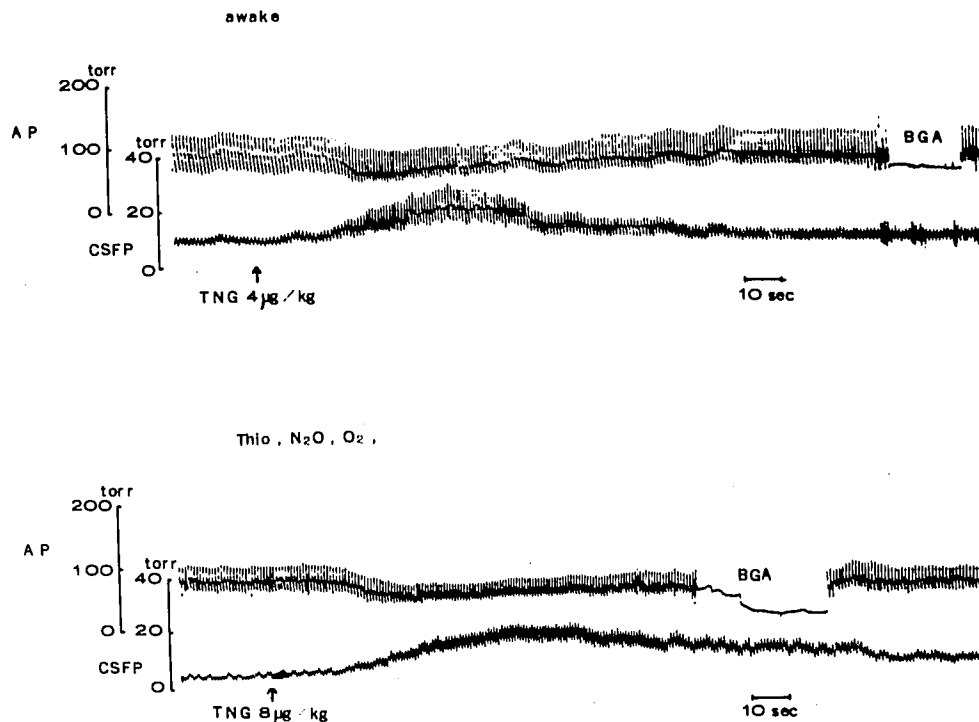


FIG. 1. Polygraph tracings of arterial blood pressure (AP) and CSFP following the administration of nitroglycerin (TNG). *Upper:* Nitroglycerin, 4 µg/kg, as iv bolus in awake, premedicated patient. *Bottom:* Nitroglycerin, 8 µg/kg, in patient anesthetized with thiamylal, nitrous oxide and oxygen. BGA = Blood gas analysis.

(fig. 1). There was no significant difference in percent changes of blood pressure and heart rate following the injection of nitroglycerin between awake subjects and anesthetized subjects. Arterial blood gas analyses in both awake and anesthetized patients at 3–4 min after the injection of nitroglycerin were not significantly different from control values (table 1).

Two of 15 awake subjects complained of headaches after the administration of nitroglycerin 8 µg/kg iv. These headaches subsided soon after CSFP decreased to the control value.

Discussion

Nitroglycerin administered as a bolus, produces consistent increases in cerebrospinal fluid pressure and decreases in arterial blood pressure in both awake and anesthetized subjects in the absence of intracranial pathology. This response is qualitatively similar to that caused by trimethaphan and sodium nitroprusside in subjects with intracranial mass lesions.¹ However, the effects of the latter two agents were somewhat variable. In a study by Turner *et al.*,¹ nitroprusside caused significant increases in ICP in normocapnic patients with elevated ICP or neurologic disorders, while in hypocapnic patients it produced no statistically significant change in ICP. In patients rendered hypotensive by trimethaphan, variable non-significant changes in ICP were found. Differences in the effects between nitroglycerin and the other

drugs in humans may be related to differences in the patients' neurologic conditions, the rate of administration, the anesthetic techniques employed, and the mode of action of the agents themselves. Lacking comparative studies between nitroglycerin and the other two agents, one can only speculate that nitroglycerin would increase ICP in every patient with intracranial hypertension as it does in patients with normal ICP.

Experimentally, in cats anesthetized with halothane, nitrous oxide and oxygen, Rogers *et al.*⁵ found that nitroglycerin, in doses of 5–20 µg/kg, produced significant increases in ICP, with larger increases in ICP correlating with larger decreases in mean arterial blood pressure. Their subsequent study⁶ in dogs anesthetized with pentobarbital showed that the intravenous bolus injection of either nitroglycerin or nitroprusside in doses of 5, 25 and 50 µg/kg, produced increases in CSFP and decreases in arterial blood pressure with both normal CSFP and elevated CSFP. The increases in CSFP appeared to be independent of changes in cerebral blood flow (CBF), since marked increases in CSFP occurred with no changes in CBF in the normal CSFP group; while with elevated CSFP both agents tended to reduce CBF.

When intracranial compliance is reduced, intracranial pulse pressure increases. The increase in intraspinal pulse pressure we observed following nitroglycerin administration may be explained by a decreased intracranial compliance secondary to the

increased CSFP. Nitroglycerin is a potent, direct systemic vasodilator of both arterial and venous vascular smooth muscle, with the effects, however, being predominant on the latter.^{7,8} The complete dilation of systemic capacitance vessels can produce a four- to fivefold increase in intravascular capacity, whereas dilation of resistance vessels can cause an increase in intravascular capacity of only 50 to 80 per cent of the initial value.[¶] These effects may be the same in intracranial vessels, since it has been suggested that the mechanism of the increase in ICP with nitroprusside is the expansion of the intracranial blood volume as a result of cerebral vasodilation.^{1,8} Nitroglycerin has also been suggested to have cerebral as well as systemic vasodilating effects.^{4,6} If the predominant effect of nitroglycerin is on intracranial capacitance vessels rather than on resistance vessels, this drug may cause even greater increases in cerebral blood volume and CSFP than does a drug such as nitroprusside.

Since thiamylal has been shown to produce significant reduction in ICP,⁹ we expected some ameliorating effects on the increase in CSFP induced by nitroglycerin. There was, however, no significant difference in the per cent increases of CSFP between awake, premedicated subjects and subjects anesthetized with thiamylal, nitrous oxide and oxygen. Since no significant difference in Pa_{CO₂} existed between the two groups, we conclude that clinical doses of thiamylal, administered 3–5 min prior to nitroglycerin cannot prevent the increase in CSFP. Because of the rapid recovery of CSFP following thiamylal, however, we cannot exclude the possibility that an interaction between thiamylal and nitroglycerin on CSFP might occur using different doses or timing.

The increases in CSFP following intravenous administration of nitroglycerin were transient in all patients studied. In the absence of intracranial pathology, this effect should not cause any harmful

sequellae in the management of systemic hypertension either in the absence or presence of anesthesia. However, in a patient with intracranial hypertension, Gagnon *et al.*⁴ observed a brisk increase in intracranial pressure following the intranasal use of nitroglycerin during halothane anesthesia. In this patient, they removed 5 ml of CSF to curtail a further increase in ICP. Therefore, special caution should be exercised in the administration of nitroglycerin to patients with reduced intracranial compliance. We recommend the use of this drug for such patients only when CSFP can be monitored continuously and rapid decompression by removal of CSF can be provided.

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