

THE EFFECT OF INTRAVENOUS KETAMINE ON CEREBROSPINAL FLUID PRESSURE

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SUMMARY

The effect of an intravenous injection of ketamine 1.1 mg/kg on the cerebrospinal fluid (c.s.f.) pressure was studied in 20 patients during nitrous oxide-oxygen and relaxant anaesthesia. In 11 patients with normal c.s.f. pathways the pressure did not alter significantly, but in 6 of 9 patients with intracranial space-occupying lesions there was a substantial rise in c.s.f. pressure. These results suggest that ketamine must be used with caution in patients with intracranial space-occupying lesions.

Ketamine has been advocated for use as an anaesthetic agent during diagnostic procedures in neurological patients by a number of writers (Corssen et al., 1969; Wilson, Fotias and Dillon, 1969). Although its hypertensive action made some authors issue a caution on its use in patients with intracerebral vascular lesions (Brown, Cole and Murray, 1970), none of these accounts mentioned the effects of ketamine on intracerebral pressure or blood flow. Evans and co-workers (1971) suggested that on occasion the administration of ketamine might be associated with undesirable levels of intrathecal pressure.

The present study was designed to compare the effects of a single intravenous injection of ketamine on the cerebrospinal fluid (c.s.f.) pressure in patients with normal c.s.f. pathways and in those with intracranial space-occupying lesions.

Because of the possibility of a rise in c.s.f. pressure in the latter patients, it was felt that it would not be reasonable to perform the study except in anaesthetized patients when using controlled ventilation.

METHODS

Two groups of patients were studied. Group 1 comprised 11 patients who were to undergo lumbar discectomy and who were assumed to have normal c.s.f. pathways. Group 2 comprised 9 patients with intracranial space-occupying lesions who were to undergo craniotomy. Informed consent was obtained for the investigation. Premedication comprised pethidine 50–100 mg and promethazine 12.5–25 mg, given intramuscularly 1 hour before anaesthetic induction which consisted of thiopentone in a dose of 200–350 mg, followed by alcuronium 10–20 mg. Prior to intubation, the lungs were ventilated with

nitrous oxide (75%) and oxygen for 3 min. After intubation, ventilation was continued using a semi-closed circle system with carbon dioxide absorption. Ventilation was based on a minute volume of 80–100 ml/kg body weight at a rate of 10–15 cycles/min using a Bennett ventilator (BA-4). An intravenous infusion was commenced and a 20-gauge cannula (Medicut) was introduced into a radial artery in patients in whom the subsequent operative procedure warranted direct pressure monitoring. In the remaining cases, arterial pressure was measured with a sphygmomanometer. In the patients in whom direct pressure readings were made, these were recorded using a Statham pressure transducer (P23Dc) and a Grass Polygraph. With the patient in the lateral position a lumbar puncture was performed with a 21-gauge needle (above the level of the disc protrusion in Group 1 patients) and c.s.f. pressure was recorded directly in the same way as the blood pressure. Care was taken to minimize c.s.f. loss. The transducer was set on a level with the spine. These procedures occupied some 20–30 min from induction of anaesthesia. After recording the pressure for 2–6 min, and ensuring a free respiratory and cardiac pulsation, ketamine 1.0–1.3 mg/kg was injected as a single dose rapidly into the intravenous drip tubing. If there was little change in arterial or c.s.f. pressure, readings were discontinued at a minimum of 6 min after the ketamine injection. When there was a response, observations were continued over a longer period. Soon after ketamine administration, an arterial blood sample was taken for blood-gas analysis. Digital compression

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over the puncture site was maintained for 10 min. No untoward sequelae were seen. At the conclusion of the observations the lumbar puncture needle was removed and the patient positioned for surgery.

Mean c.s.f. pressures have been taken as the end-expiratory diastolic pressure $+\frac{1}{3}$ c.s.f. pulse pressure. Mean systemic arterial pressure was similarly calculated as end-expiratory diastolic pressure $+\frac{1}{3}$ of the difference between systolic and diastolic pressures. After c.s.f. pressure, in mm H₂O had been converted to mm Hg, mean cerebral perfusion pressure was obtained by subtracting c.s.f. pressure from mean arterial pressure.

RESULTS

C.s.f. pressure. In the Group 1 (lumbar discectomy) patients, there was no consistent trend toward any change in c.s.f. pressure although rises did occur in individual cases. The results are shown in tables I, II and figure 1. Comparing the pressure at the time of administration of ketamine with the maximum pressure recorded after this in each case, the mean maximum pressure rise was 14 ± 6 (SE) mm H₂O. This and subsequent similar calculations, compared the initial pressure with the maximum attained thereafter irrespective of the time at which it occurred. This change was not significant when subjected to a paired Student *t*-test. In the Group 2 (intracranial lesion) patients, the c.s.f. pressure rose to a substantial degree in 6 of the 9 patients. The

mean maximum pressure rise was 150 ± 61 (SE) mm H₂O. This change was statistically significant at the 5% level of probability using a paired Student *t*-test. In one case two records were taken from the same patient, a boy of 11 with a tumour in the region of the third ventricle. On the first occasion when ketamine induced a marked rise in c.s.f. pressure (from 170 to 600 mm H₂O after 10 min), a Holter valve was inserted to establish c.s.f. drainage to the right atrium. Prior to craniotomy 2 weeks later, ketamine did not produce any changes in the intrathecal pressures (pressures ranged from 220 to 200 mm H₂O). Of the other two cases in this group whose c.s.f. pressure did not change, one was a young man with a small frontal glioma, and the other a man with a simple parietal subarachnoid cyst.

Arterial pressure (tables I, II; fig. 1). Although the mean changes were relatively small, there was an increase in arterial pressure following ketamine. In the Group 1 patients the maximum mean rise was 7 ± 3 (SE) mm Hg and in the Group 2 patients, 24 ± 10 (SE) mm Hg. Using a paired Student *t*-test the changes were significant at between 2 and 5% and at 1% levels of probability respectively.

Cerebral perfusion pressures (table III). These were calculated, as described earlier, in the intracerebral lesion patients. Comparing mean pressures at the time of ketamine administration with the mean pressures at time of maximum c.s.f. pressure, there was a change in mean cerebral perfusion pres-

TABLE I. *Effects of ketamine on c.s.f. and arterial pressures. Mean value \pm standard error of the mean.*

	Diagnosis	No. of cases	Weight (kg)	Ketamine dose (mg)	Paco ₂ (mm Hg)
Group 1	Discectomy	11	69.5 ±3.0	78 ±3	37 ±2
Group 2	Intracerebral lesion	9	60.4 ±4.5	73 ±5	38 ±2

Time in min related to ketamine dose									
	2	0	2	4	6	8	10	12	
c.s.f. pressure (mm H ₂ O)									
Group 1	109 ±16	103 ±15	97 ±17	106 ±18	109 ±16	105* ±16			
Group 2	260 ±76	229 ±50	242 ±41	297 ±52	324 ±52	359† ±69	346† 68	346° 63	

Arterial pressure (mm Hg)									
Group 1	111 ±6	112 ±4	115 ±5	116 ±5	117 ±5	121* ±5			
Group 2	116 ±5	118 ±6	123 ±7	127 ±7	132 ±7	133† ±8	131† ±7	133* ±7	

Number of readings: °=5; *=6; †=8

TABLE II. Pressure at time of ketamine injection compared with maximum pressure thereafter.

C.s.f. pressure		
Group 1	Change	= $+14 \pm 6$ mm H ₂ O
	<i>t</i>	= 1.826; $P > 0.10$
Group 2	Change	= $+150 \pm 61$ mm H ₂ O
	<i>t</i>	= 2.447; $0.05 > P > 0.02$
Arterial pressure		
Group 1	Change	= $+7 \pm 3$ mm Hg
	<i>t</i>	= 2.367; $0.05 > P > 0.02$
Group 2	Change	= $+24 \pm 10$ mm Hg
	<i>t</i>	= 3.500; $0.02 > P > 0.01$

Statistical comparison by paired Student *t*-test.
Values stated are means \pm standard error of mean.

sure from 74 ± 7 (SE) mm Hg to 72 ± 6 (SE) mm Hg. It should be noted that in two patients in whom there was a marked rise in c.s.f. pressure there was a fall in cerebral perfusion pressure in spite of the accompanying rise in systemic arterial pressure (115–81 mm Hg and 68–41 mm Hg).

Pulse rate (fig. 1). There was a slight rise in pulse rate in both groups. The change in mean values was approximately 10 beats/min.

Ventilation. As determined by the blood-gas measurements (table I) carried out after ketamine administration, the Group 1 patients had P_{aCO_2} values ranging from 25 to 45 mm Hg with a mean value of 37 ± 2 (SE) mm Hg. In Group 2, the range was 32–47 mm Hg with a mean value of 38 ± 2 (SE) mm Hg.

Side effects. There were no anaesthetic or surgical sequelae which could be related to the use of ketamine. All patients were specifically questioned, with regard to dreams or hallucinations, on the day following surgery. No positive reports were obtained.

DISCUSSION

Since the suggestion by Evans and associates (1971) that ketamine administration might be associated with a rise in c.s.f. pressure, some confirmatory reports have appeared. Gardner, Olsen and Lichtiger (1971) examined several patients prior to spinal anaesthesia and found that intravenous injection of ketamine produced rises in both mean blood pressure and c.s.f. pressure. Whyte and associates (1972) studied the effects of ketamine in two patients, one with and one without raised intra-

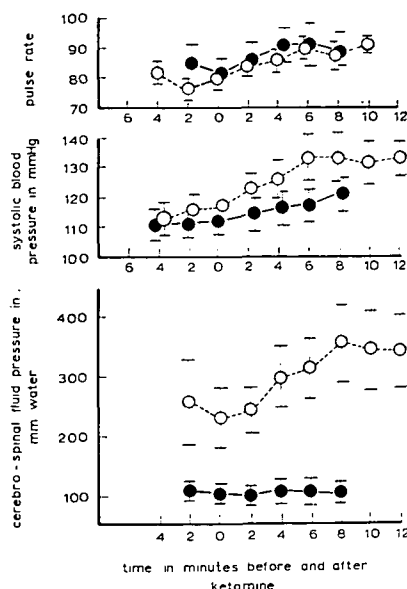


FIG. 1. Comparison of pulse, arterial pressure and c.s.f. pressure changes in "normal" patients (Group 1) and in patients with intracerebral space-occupying lesions (Group 2).

— = Group 1; ---- = Group 2.

Values plotted = mean \pm standard error of mean.

cranial pressure. They were able to demonstrate a marked rise in intraventricular pressure following intravenous injection of ketamine in the patient with raised intracranial pressure. They also noted reduction of this response with thiopentone, and comment that the short duration of this modification is related to the time taken for distribution of the thiopentone. Dawson, Michenfelder and Theye (1971) studied the effects of ketamine on c.s.f. pressure and cerebral blood flow in dogs and the manner in which the observed rises in both were prevented by thiopentone given immediately before the ketamine. Because of the time between the injection of thiopentone for induction of anaesthesia and the administration of ketamine in the present study, it is unlikely that thiopentone greatly altered the pattern of the c.s.f. pressure changes.

The magnitude of the changes in both c.s.f. and arterial pressures in the present study were less than those reported by Gardner, Olsen and Lichtiger

TABLE III. Maximum effect of ketamine on cerebral perfusion pressure (mean values \pm standard error of the mean).

Perfusion pressure at time of ketamine administration	74 ± 7 mm Hg
Perfusion pressure at time of maximum c.s.f. pressure following ketamine	72 ± 6 mm Hg

(1971). The mean dose of ketamine in the present study was less than in either of the reports mentioned earlier (1.1 mg/kg as opposed to 2 mg/kg). In addition, it is probable that the response was reduced by general anaesthesia. Bovill and associates (1971) found that the effect of ketamine on arterial pressure was greater when the drug was used as a sole agent than when it was used in combination with nitrous oxide.

The rise in c.s.f. pressure associated with ketamine was minimal in the "normal" anaesthetized subjects but considerably greater in those patients with altered c.s.f. flow pathways as a consequence of an intracerebral lesion. The modification of the response to ketamine by establishment of c.s.f. drainage through a Holter valve strongly supports this finding. As the mean values for P_{aCO_2} were similar (and near normal) in both groups of patients, it is unlikely that ventilation played a part in the different c.s.f. pressure responses in the two groups. It is also noteworthy that the rise in arterial pressure associated with ketamine was greater in the patients with space-occupying lesions.

The reflection of intracerebral pressure changes in the subarachnoid space suggests that there is a rise in brain volume, presumably as a result of increased cerebral blood flow. Dawson, Michenfelder and Theye (1971) have demonstrated that this is so in studies in dogs and suggest that ketamine may produce this effect by acting as a cerebral metabolic stimulant and vasodilator. Takeshita, Okuda and Sari (1972) suggest that ketamine increases cerebral blood flow but does not significantly alter cerebral metabolism in normal man. They also recorded an increase in cerebral perfusion pressure. By contrast, halothane causes a fall in arterial pressure and a rise in cerebral blood flow in normocapnic subjects (Freeman, 1969) by a process of cerebral vasodilatation. In parallel with the present study, Jennett and associates (1969) showed that the effect of inhalational anaesthetic agents in raising c.s.f. pressure was more marked in patients with intracranial space-occupying lesions. However, comparing the effects of halothane and of ketamine on c.s.f. pressure, it is seen that while they are similar in this respect, halothane tends to cause a fall in systemic blood pressure, while ketamine causes a rise. In the present study this blood pressure rise has a similar time course to the c.s.f. pressure rise in patients with intracranial lesions. Calculation of the changes in cerebral perfusion pressure by the method of Fitch and associates (1969) suggests that in general this is maintained,

although falls did occur in the patients who showed the greatest rise in c.s.f. pressure after ketamine administration.

There do not appear to be any published studies which show whether the rise in arterial pressure would, to any degree, protect areas of marginally ischaemic brain against the adverse effects of a further rise in intracerebral pressure. In addition, the effect of ketamine on c.s.f. pressure and cerebral blood flow in the presence of different levels of arterial carbon dioxide has not been clearly established.

In the light of current knowledge and of the changes in c.s.f. pressure demonstrated in this and other studies, it is suggested that intravenous injection of ketamine should be used with caution in patients who are known to have an intracerebral space-occupying lesion or raised intracranial pressure.

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REFERENCES

- Bovill, J. G., Coppel, D. L., Dundee, J. W., and Moore, J. (1971). Current status of ketamine anaesthesia. *Lancet*, **1**, 1285.
- Brown, T. C. K., Cole, W. H. J., and Murray, G. H. (1970). Ketamine: a new anaesthetic agent. *Aust. N.Z. J. Surg.*, **39**, 305.
- Corssen, G., Groves, E. H., Gomez, S. and Allen, R. J. (1969). Ketamine: its place in anaesthesia for neurosurgical diagnostic procedures. *Anesth. Analg. Curr. Res.*, **48**, 181.
- Dawson, B., Michenfelder, J. D., and Theye, R. A. (1971). Effect of ketamine on canine cerebral blood flow and metabolism: modification by prior administration of thiopental. *Anesth. Analg. Curr. Res.*, **50**, 443.
- Evans, J., Rosen, M., Weeks, R. D., and Wise, C. (1971). Ketamine in neurosurgical procedures. *Lancet*, **1**, 40.
- Fitch, W., Barker, J., Jennett, W. B., and McDowall, D. G. (1969). The influence of neuroleptanalgesic drugs on cerebrospinal fluid pressure. *Brit. J. Anaesth.*, **41**, 800.
- Freeman, J. (1969). The cerebral circulation in anaesthesia. *Int. Anesthesiol. Clin.*, **7**, 327.
- Gardner, A. E., Olsen, B. E., and Lichtiger, M. (1971). Cerebrospinal-fluid pressure during dissociative anaesthesia with ketamine. *Anesthesiology*, **25**, 226.
- Jennett, W. B., Barker, J., Fitch, W., and McDowall, D. G. (1969). Effects of anaesthesia on intracranial pressure in patients with space-occupying lesions. *Lancet*, **1**, 61.
- Takeshita, H., Okuda, Y., and Sari, A. (1972). The effects of ketamine on cerebral circulation and metabolism in man. *Anesthesiology*, **36**, 69.
- Wilson, G. H., Fotias, N. A., and Dillon, J. B. (1969). Ketamine: a new anesthetic for use in pediatric neuro-radiologic procedures. *Amer. J. Roentgenol.*, **106**, 434.
- Whyte, S. R., Shapiro, H. M., Turner, P., and Harris, A. B. (1972). Ketamine-induced intracranial hypertension. *Anesthesiology*, **36**, 174.

EFFET DE L'ADMINISTRATION INTRAVEINEUSE DE KETAMINE SUR LA PRESSION DU LIQUIDE CEPHALO-RACHIDIEN

SOMMAIRE

L'effet d'une injection intraveineuse de 1,1 mg/kg de Kétamine sur la pression du liquide céphalo-rachidien, a été étudié chez vingt malades au cours d'une anesthésie mettant en oeuvre le mélange protoxyde d'azote/oxygène et des myorelaxants. Chez les onze malades dont les caractéristiques du LCR étaient normales, la pression de ce dernier ne subit aucune altération significative, mais chez six malades sur neuf ayant présenté des lésions à type de compression intracrânienne, on nota une augmentation substantielle de la pression du LCR. Ces résultats suggèrent une utilisation prudente de la Kétamine chez des malades présentant des lésions à type de compression intracrânienne.

ÜBER DIE WIRKUNG EINES INTRAVENÖSEN KETAMINS AUF DEN DRUCK DES LIQUOCEREBROSPINALIS

ZUSAMMENFASSUNG

An zwanzig Patienten wurde während einer Narkose mit Lachgas und Relaxantien die Wirkung einer intravenösen Injektion von Ketamin 1,1 mg/kg auf den Druck des

Liquorcerebrospinalis (c.s.f.) untersucht. Bei elf Patienten mit normalen Verhältnissen im Bereich des Liquorraumes veränderte sich der Druck nicht significant. Jedoch bei sechs von neun Patienten mit raumfordernden intracraniellen Prozessen ergab sich ein deutlicher Druckanstieg des Liquorcerebrospinalis. Diese Untersuchungsergebnisse lassen erkennen, daß die Anwendung von Ketamin bei Patienten mit raumfordernden intracraniellen Prozessen mit Vorsicht zu erfolgen hat.

EFFECTO DE LA CETAMINA INTRAVENOSA SOBRE LA PRESION DEL LIQUIDO CEFALORRAQUIDEO

RESUMEN

El efecto de una inyección intravenosa de 1,1 mg/kg de cetamina sobre la presión del líquido cefalorraquídeo (c.s.f.) fue estudiado en veinte pacientes durante la anestesia por óxido nitroso-oxígeno y relajante. En once pacientes con vías normales para el c.s.f. no hubo alteración significativa de la presión, pero en seis pacientes de nueve con lesiones ocupadoras de espacio intracraneal hubo una elevación sustancial de la presión del c.s.f. Estos resultados sugieren que la cetamina debe ser utilizada con cuidado en pacientes con lesiones ocupadoras de espacio intracraneal.

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FRIDAY, FEBRUARY 16. Ordinary Meeting at Liverpool Medical Institution, open to all members of the Institution.

Speakers: Professor J. W. Dundee (Queen's University of Belfast), Dr D. L. Coppel (Royal Victoria Hospital, Belfast): "Trauma and Civil Disturbance".

FRIDAY, MARCH 16. Ordinary Meeting at Liverpool Medical Institution.

Papers will be presented in competition for the Registrars' Prize.

THURSDAY, APRIL 12. Joint Meeting with the Anaesthetic Section of the Manchester Medical Society, in Liverpool.

Speakers: Dr Margaret Dodson (Manchester), Dr A. A. Gilbertson (Liverpool): Subjects to be announced later.

THURSDAY, MAY 10. The Forty-first Annual General Meeting at the Liverpool Medical Institution followed by a social function.

All meetings at 8 p.m.