Effect of diltiazem-induced hypotension on normal and increased intracranial pressure of cats

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The commonly used vasodilators sodium nitroprusside and nitroglycerin increase intracranial pressure (ICP) and cause tachycardia. Since diltiazem is also a vasodilator, we designed this experiment in cats to study its effect on intracranial pressure and heart rate (HR). Twelve cats were assigned to two equal groups. One group had normal ICP (N-ICP), while in the other the ICP was raised artificially (AR-ICP) by placing a balloon into the intracranial extradural space. Both groups received an infusion of diltiazem to decrease the mean blood pressure (BP), which was maintained 30 per cent below the baseline value for 15 minutes.

Diltiazem caused no significant change in ICP (5.7 ± 1 to 6.7 ± 1.5 mmHg, $p < 0.01$) in cats with N-ICP while in cats with AR-ICP, the increase from 26.9 ± 0.5 to 34.0 ± 1.9 mmHg was significant ($p < 0.006$). HR decreased significantly during the diltiazem infusion in both groups.

Key words
BRAIN: intracranial pressure; HYPOTENSION INDUCED: diltiazem.

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Commonly used vasodilators like sodium nitroprusside (SNP) increase intracranial pressure (ICP) and are not recommended for patients with intracranial hypertension.[1] Diltiazem is a slow channel calcium blocker possessing vasodilating properties[2] and its effects on ICP of dogs with acute hydrocephalus has been recently reported.[3] It has been suggested that a more clinically relevant model of a space occupying lesion can be provided by the use of an intracranial epidural balloon rather than a communicating hydrocephalus.[4] We therefore designed an experiment in which the ICP was increased by placing an intracranial epidural balloon in cats, to mimic a space occupying lesion.

Methods

Twelve cats (2.5–3.5 kg) were each anaesthetised with isoflurane, intubated utilizing endotracheal tubes lubricated wtih tetracaine ointment and ventilated with a Harvard animal respirator. Femoral vessels were cannulated for drug administration, monitoring of BP and blood gases analyses. The cats were then placed in the sphinx position using a stereotactic frame with the interaural plane five inches above the level of the chest. The scalp and underlying muscles were dissected and a 5 mm hole was trephined in the left parietal area of all cats. A 7F catheter was threaded into the subarachnoid space and connected to a pressure transducer for continuous monitoring of the ICP. The cats were assigned into equal sized groups; one with N-ICP and the other having an artificially raised ICP (AR-ICP). In the AR-ICP group a 10 F Foley catheter was placed in the epidural space through a 5 mm trephined-hole in the right parietal area. Both trephined holes were sealed airtight with bone wax.

TABLE Results (mean ± SE).

	Normal ICP group (n = 6)				*Increased ICP group (n = 6)*			
	BP	*ICP*	*CPP*	*HR*	*BP*	*ICP*	*CPP*	*HR*
Control	124 ± 3	5.7 ± 1	118 ± 3	223 ± 6	134 ± 6	26.9 ± 0.5	107 ± 7	220 ± 23
Diltiazem	85 ± 2*	6.7 ± 1.5	79 ± 3*	197 ± 8*	94 ± 4*	34.0 ± 1.9*	60 ± 5*	182 ± 12*
Post infusion	111 ± 3*	5.8 ± 1	106 ± 4*	215 ± 8	119 ± 5*	28 ± 1.5	91 ± 4*	218 ± 8

*$p < 0.05$.
Blood pressure (BP), intracranial pressure (ICP, cerebral perfusion pressure (CPP) (CPP = BP-ICP) and heart rate (HR).

Upon completion of surgery, the operative sites were infiltrated with 2–3 ml of 0.5 per cent bupivacaine and isoflurane was discontinued. Anaesthesia was then maintained with nitrous oxide in 30 per cent oxygen and intermittent doses of pancuronium ($0.5\ mg \cdot hr^{-1}$). Once the animals were stabilized under nitrous oxide/oxygen anaesthesia, the experiment was initiated. The balloon of the Foley catheter was slowly inflated with increments of 0.1–0.2 ml of water at five-minute intervals until the ICP remained constant at about 30 mmHg. The BP, HR, ICP, EKG and end-tidal CO_2 were monitored continuously using a Beckman R612 (eight channel) physiological recorder. Arterial blood gases were analyzed (Corning 168 pH/gas analyzer) every hour. The $PaCO_2$ was maintained at 30 ± 2 mmHg (normocarbia for cats 28–32 mmHg[5]), the PO_2 above 100 mmHg and pH at 7.35 ± 0.05. Rectal and brain temperatures were monitored and maintained at 37 ± 0.05° C. Lactate Ringer's solution was infused intravenously at $5\ ml \cdot kg^{-1} \cdot hr^{-1}$ to offset insensible fluid loss incurred during the procedure.

One hour after discontinuing isoflurane and in the presence of stable vital signs, the dose of diltiazem required for each cat to decrease the BP approximately 30 per cent was determined by stair step design. Once again the animal was permitted to stabilize (approximately one hour) before the predetermined dose of diltiazem was infused over a period of 15 minutes. The BP, HR, EKG (PR interval) and the peak ICP were determined before, during and 30 minutes after discontinuation of the infusion. All observations were made at the end of expiration; the zero level for the ICP was referenced to a fixed point at the level of the external auditory meatus. Control and post infusion BP, HR, and the ICP were compared and analyzed by Student's paired t-test. P values < 0.05 were considered significant.

Results

The results are summarized in the Table and in the Figure. Diltiazem ($100–300\ \mu g \cdot kg^{-1} \cdot min^{-1}$) produced dose dependent hypotension. During the period of hypotension, the cats with N-ICP experi-

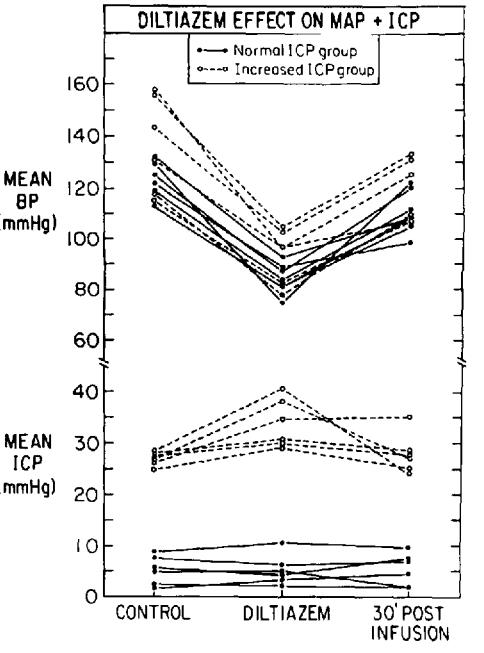

FIGURE 1 Mean blood pressure (BP) and intracranial pressure (ICP) of individual cats during control period, during diltiazem infusion and 30 minutes post infusion.

enced no change in ICP; 5.7 ± 1 to 6.7 ± 1.5 mmHg ($p < 0.1$). In the cats with AR-ICP, ICP increased significantly ($p < 0.006$), from 26.9 ± 0.5 to 34.0 ± 1.0 mmHg. In both groups the ICP returned to a steady state within 30 minutes following discontinuation of the diltiazem infusion.

The HR significantly decreased in both groups ($p < 0.01$) during the period of diltiazem induced hypotension, but returned to near control rates on discontinuation of the infusion. The PR interval in one cat increased from 0.1 to 0.36 msec during the infusion period and remained prolonged for 30 minutes following termination of the infusion; two cats experienced transient ventricular arrhythmias.

The peak hypotensive effect of diltiazem occurred in 202 ± 55 seconds following initiation of the diltiazem infusion. The BP gradually reached a steady state at 660 ± 130 seconds but remained significantly below the control value ($p < 0.008$) even after 30 minutes. There was no evidence of tachyphylaxis, rebound hypertension or metabolic acidosis during or following the infusion.

Discussion

Diltiazem, verapamil and nifedipine are representative of the slow channel calcium blockers currently available. All are vasodilators; diltiazem is similar to verapamil, but both are less potent vasodilators than is nifedipine. In addition, diltiazem, like verapamil has negative inotropic, chronotropic and dromotropic effects.[2] Diltiazem dilates spastic cerebral vessels and has been useful in cerebral resuscitation.[6,7] Nifedipine and verapamil-induced hypotension has been shown to increase ICP in cats with intracranial hypertension.[8,9]

Diltiazem caused no significant change in the ICP of N-ICP cats, while the ICP significantly increased in the cats with preexistant intracranial hypertension ($p < 0.008$) (Figure). The arterial and venodilatation of the cerebral vessels is presumed to be the cause for the increase in ICP as with SNP and nitroglycerin (NTG). Similar trends were observed in dogs anaesthetised with pentobarbitone.[3] Although there was a statistically significant increase in the ICP of dogs with intracranial hypertension in their study, Mazzoni *et al.* questioned the clinical significance. Our findings demonstrated a statistically and clinically significant increase of ICP in the cats with intracranial hypertension. Mazzoni *et al.* reported a smaller rise in ICP but this is related to a number of differences between the two experimental models. They utilized a more invasive intraventricular route for ICP monitoring instead of the subarachnoid route. Bilateral ventricular distension was used in their study instead of a unilateral focal mass lesion as used in our study to raise the ICP. Mazzoni *et al.* subjected the same animal to the effect of diltiazem twice; the same animal was utilized for the normal ICP group and again in the increased ICP group. These factors may have interfered with the cerebrovascular autoregulation of the animal to a greater extent than our cat model.[10,11] Pentobarbitone anaesthesia, and the use of a different species may be additional reasons for the disparity in the results.

Diltiazem produced a dose-dependent hypotension, but the onset and recovery are much slower than described for SNP.[9] The BP consistently remained 10 ± 2 per cent less than the control value even 30 minutes following discontinuation of diltiazem infusion. Diltiazem depresses the sinoatrial node, decreases the HR and thus prevents the reflex tachycardia associated with hypotensive state. Tachycardia, seen during SNP or NTG infusion is caused by the reflex response of the baroreceptors, and tends to raise BP.

As in our study, electrophysiological effects on the cardiac conduction have been observed with diltiazem, both in animal studies and clinical observations.[2,12] The magnitude of this depressant effect on the conducting tissue is greater in halothane anaesthetised swine[2] than in pentobarbitone anaesthetised dogs.[13] The dose of diltiazem and the concomitant administration of other cardiac depressant anaesthetics seems to determine the frequency and the magnitude of the effect of diltiazem on the conducting system.

Barbiturates and ketamine anaesthetics were avoided in the experiment because of their effect on intracranial compliance. Isoflurane was discontinued at least an hour before the actual study commenced in order to offset any effects on cerebral haemodynamics. The concentration of nitrous oxide (70 per cent) used in this experiment provides adequate analgesia and sedation in cats[14,15] and has minimal effects on ICP.

The infusion method was chosen for this study because sustained hypotension was produced; this

was ideal for recording the changes in the ICP as hypotension was induced, sustained and when BP returned to control levels. It also facilitated the evaluation of rebound hypertension; finally, SNP and NTG are administered by the infusion technique in clinical practice. Initially, the stair-step design was utilized to determine the dose required to decrease the BP by approximately 30 per cent. When this predetermined dose was infused, the BP consistently decreased by 30 per cent and reached a plateau in all the cats.

Diltiazem has desirable attributes such as the absence of tachycardia, tachyphylaxis and rebound hypertension and it offers protection against cerebral ischaemia. However, onset of action and recovery are slow and the adverse effect on cardiac conducting tissue diminishes diltiazem's usefulness as a hypotensive agent. Additionally, there is a significant increase in intracranial pressure of cats with existing intracranial hypertension. An increase in the intracranial pressure for patients on the compromised portion of the intracranial compliance curve will further decrease the perfusion of brain or may cause herniation of brain tissue. Caution must always be exercised when extrapolating results from animal studies to humans; these results, however, suggest possible deleterious effects diltiazem may cause patients with intracranial hypertension.

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Résumé

Les vasodilatateurs communément utilisés tels que nitroprussiate de soude et de nitroglycérine augmentent la pression intracrânienne (ICP) et provoquent la tachycardie. Etant donné que le diltiazem est aussi un vasodilatateur on a crée un modèle expérimental d'étude chez le chat de l'effet du diltiazem sur la pression intracrânienne et la fréquence cardiaque. Douze chats ont été divisés en deux groupes égaux. Le premier groupe présentait une pression intracrânienne normale alors que chez le deuxième groupe on augmenta d'une façon artificielle la ICP en plaçant des ballons dans l'espace intracrânien et extradural. Les deux groupes de chats ont reçu une infusion de diltiazem afin de diminuer la pression artérielle moyenne qui était maintenue à 30 pour cent en bas de la valeur de base pour 15 minutes.

Le diltiazem n'a pas augmenté d'une façon significative la pression intracrânienne chez le premier groupe à pression intracrânienne normale (5.7 ± 1 à 6.7 ± 1.5 mmHg) ($p < 0.1$). Pour le deuxième groupe l'augmentation était de 36.8 ± 0.5 à 34.0 ± 1.9 mmHg et était significative ($p < 0.006$). La fréquence cardiaque a diminué significativement dans les deux groupes.