HUMAN BEHAVIOURAL AROUSAL INDUCED BY DOPAMINE

Cerebral arterial constriction (vasospasm) commonly follows subarachnoid haemorrhage (SAH) due to rupture of an intracranial aneurysm (Allcock & Drake, 1965). It also occurs postoperatively and then vasospasm is associated with a high morbidity and mortality (Adams, Loach & O'Laoire, 1976). There have been many attempts to alleviate vasospasm with vasodilator drugs. Propranolol, papaverine, phentolamine and phenoxybenzamine have all been tested without any substantial improvement in prognosis or mortality.

Dopamine increases cerebral blood flow (CBF) in animals (von Essen, 1972; 1974) and relaxes human and baboon cerebral vessels *in vitro* (Boullin, Adams, Mohan, Green, Hunt, Du Boulay & Rogers, 1977). When injected intracisternally into anaesthetised baboons dopamine causes dilatation of the major cerebral arteries with α -adrenergic receptor mediated constriction in higher doses. On the basis of these observations we are currently attempting to relieve vasospasm in SAH patients by intracranial perfusion of dopamine through silicone rubber tubing implanted at the time of microneurosurgery for aneurysm clipping (Boullin *et al.*, 1977).

During the course of studies with fourteen SAH patients we observed an arousal phenomenon immediately dopamine infusion was begun. We now report the results of these investigations.

Fourteen SAH patients received intracerebral dopamine through 1.4 mm bore silicone rubber tubing. The infusion flow rate varied between 5 and 10 ml/h with higher infusion rate of up to 0.4 ml/min (25 ml/h) for not more than 5 min (2.1 ml infused). In most patients the following protocol was followed:

Initially dopamine was infused at 0.4 ml/min for 5 min in order to induce arousal and check for continuous efflux. This was followed by short periods of high rate infusion described below. Thereafter the rate was reduced to 0.1–0.2 ml/min for up to 25 h. Dopamine concentrations ranged from 1 to 1000 μ g/ml so that the dopamine infusion rate varied from 0.1 to 400 μ g/min. Intracranial perfusion was only continued if outflow through a similar silicone rubber tube was established in the first 5 min.

Arousal was noted in the first subject (30 year old female) who received 1 mg dopamine HCl in 200 μ g aliquots via a single catheter with the tip placed at the bifurcation of the internal carotid artery. The patient was sedated with diazepam for carotid angiography immediately (20 min) following aneurysm surgery. When 0.2 ml saline was injected intracerebrally over 30 s there was no change in the patient's degree of arousal. However immediately 0.2 ml of dopamine was infused the patient opened her eyes and spoke

logically and clearly. She turned her head to inspect the room and enquired about the angiographic procedure. She also raised her head to inspect her hands and had to be lightly restrained.

As soon as the infusion was terminated the arousal effect disappeared within 30 s.

The effect was observed in nine out of fourteen patients with dopamine concentrations in the range 100–1000 μ g/ml. The most dramatic effects were observed during infusion of a 32 year old male with 500 μ g/ml dopamine at the rate of 2.4 ml/min (1.2 mg/min for 2–5 min periods). This rapid infusion rate was superimposed on a slower infusion rate of 0.1–0.2 ml/min (50–100 μ g/min) which had been carried out for 20 h commencing 2 h after the termination of neurosurgery. During the slow infusion there was no arousal but angiographic evidence for partial reversal of immediate post-operative vasospasm. At this time 2–20 h postoperative the patient was apparently sleeping but was aroused with difficulty. He did not respond to questioning as to his location and condition.

This patient awoke within 30 s of receiving intracranial dopamine at the rate of 1.2 mg/min. He looked around and replied clearly and logically to questioning. He was aware of his location, injury but not the day of the week. The rapid infusion rate was reduced after 2.5 min and the patient returned to sleep within 90 s and could not easily be aroused.

The rapid infusion protocol was repeated 3 times for 2–5 min periods over the next hour. On each occasion the patient awoke within 60 s, responded to the same set of questions and then returned to sleep and a low level of arousal within 90 s of termination of the infusion.

On the last occasion the patient showed evidence of recall in the form of impatience on being repeatedly questioned; he asked why it was necessary.

Similar effects were noted in seven other patients who received dopamine at rates exceeding 100 μ g/min.

Arousal was not due to saline infusion and appeared to be independent of the infusion rate since it was observed with 2 mg/ml infused at 0.2 ml/min (400 μ g/min) and 0.5 mg/ml infused at 2.4 ml/min (1.2 mg/min).

There do not appear to be any other reports of behavioural arousal in man with dopamine. On the other hand such phenomena have been described in animals following L-dopa in reserpinised rats (Blaschko & Chrusciel, 1960); and administration of L-dopa plus a monoamine oxidase inhibitor induced a well-defined pattern of behaviour in rats (Green & Kelly, 1976).

Also in baboons we have observed a more rapid awakening of animals anaesthetised with halothane. Whereas after 2–4 h anaesthesia, recovery to prone posture normally takes at least 20 min, in animals which have received 10–500 µg/kg dopamine by single intracisternal injection, recovery took 5–10 min in 16 experiments.

The mechanism of dopamine induced arousal in man is not known; changes in calibre of major cerebral arteries did occur after dopamine, but not with the rapidity of either the appearance of disappearance of the arousal phenomenon (Boullin *et al.*, 1977). In our view therefore arousal is unlikely to be due to rapid changes in cerebral arterial calibre. In all investigations dopamine was infused to within 1–2 cm of the aneurysm clip which was invariably within 2 cm of the Circle of Willis. The adjacent brain structures include the frontal lobes and diencephalon including the hypothalamus. As vomiting did not occur the drug did not appear to reach the chemoreceptor trigger zone in the medulla oblongata. Boullin *et al.*, (1977) reported that only 10–40% of infused dopamine was recovered in the outflow tube; it is therefore extremely likely that some of the dopamine was taken up into the brain neurones in addition to being disposed of by diffusion through the CSF and metabolism. However there is no information as to whether the amine involved dopaminergic, serotonergic or nor-adrenergic neurones or neurones containing other transmitters.

The last point to be considered is the clinical usefulness of intracranial dopamine administration. Currently we are investigating the place of dopamine as a treatment of vasospasm following aneurysm surgery (Boullin *et al.*, 1977). Also vasospasm may occur in head trauma (MacPherson & Graham, 1978); but justification for burr holes and catheter insertion is not easily made in other circumstances. On the other hand in comatose patients from drug overdose or other causes such a procedure might be justified.

In any event we have found that intracranial

dopamine perfusion for up to 25 h has not produced an untoward effect in patients with vasospasm, and therefore further investigation of dopamine arousal phenomena should be made when clinical conditions warrant.

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DECLINE IN CHLORDIAZEPOXIDE PLASMA LEVELS DURING FIXED-DOSE THERAPY OF ALCOHOL WITHDRAWAL

Chlordiazepoxide is among the most commonly administered drugs for the symptomatic management of the alcohol withdrawal syndrome (Sellers & Kalant, 1976). Studies of chlordiazepoxide and metabolite cumulation during multiple dosing in persons without medical disease suggest that once 'steady-state' is

reached levels are relatively stable (Greenblatt, Shader, MacLeod & Sellers, 1978a; Greenblatt, Shader, Franke & Harmatz, 1978b). Such slow cumulation can be associated with delayed drug efficacy or late toxicity such as drowsiness. To avoid these potential problems, dosage of the drug is often