Acta Neurol. Scandinav. 52, 331–334, 1975

SHORT COMMUNICATIONS

Department of Neurology and Department of Radiotherapeutics,
University of Göteborg, Göteborg, Sweden.

DEXAMETHASONE EFFECT ON BLOOD-BRAIN BARRIER DAMAGE CAUSED BY ACUTE HYPERTENSION IN X-IRRADIATED RABBITS

Christian Blomstrand, Barbro Johansson and Bengt Rosengren

ABSTRACT

Unilateral X-ray exposure of brain increases the vulnerability of cerebral vessels to acute hypertension in the brain hemisphere exposed to radiation. A preventive effect of dexamethasone was observed when treatment with the drug was started before irradiation; but also when the drug was given 24 h before acute hypertension was induced, 1 week after irradiation.

Since they were introduced to reduce brain tumour oedema (*Galicich & French* 1961), glucosteroids have frequently been used in the treatment of brain oedema from different causes. Steroids also reduce leakage of plasma across vascular walls, thus diminishing the degree of oedema after radiofrequency-induced heat lesions (*Rovit & Hagan* 1968), and cold-induced lesions (*Maxwell et al.* 1971). Controversial reports of the effect of corticosteroids on experimental cerebral infarction are given by, for example, *Lee et al.* (1974) and *McGraw et al.* (1974). The effect of steroids on brain oedema in man and experimental animals is reviewed in a recent publication (*Reulen & Schürmann* 1972).

In an earlier publication, we have demonstrated scattered blood-brain barrier lesions in acute hypertension in rabbits. After unilateral X-ray exposure of brain, there was a marked increase in the vulnerability of cerebral vessels to blood pressure increase in the brain hemisphere exposed to radiation (*Blomstrand et al.* 1975). As a next step, we have now investigated whether dexamethasone modifies these lesions.

Materials and methods

Albino rabbits weighing 1.7–2.0 kg were used. Animals to be irradiated were given a slight barbiturate anaesthesia, and the left half of the brain was irradiated by a single surface dose of 3000 R, given at 300 R/min (200 kV filter 0.2 mm Cu, HVL 0.9 mm Cu). The field size was 3×6 cm.

Experimental group 1: Seven rabbits received 0.25 mg dexamethasone intramuscularly twice daily for 8 days, starting from the day before X-irradiation. On

This work was supported by the Swedish Medical Research Council (B74–12p–3927–02B)

the last day, acute hypertension was induced by an intravenous injection of metaraminol (Aramine®) (0.1–0.2 mg/kg in saline). The mean arterial blood pressure was monitored by continuous electromanometrical recording from a femoral artery. Prior to the blood pressure increase, Evans blue was given intravenously (5 ml 2 per cent solution per kg body weight). The rabbits were sacrificed 30 min after the metaraminol injection by perfusion through the heart with 10 per cent neutral formalin, after a brief rinse with saline. Frozen sections (10 μm) were cut from stained and unstained areas, mounted in 50 per cent glycerin in water, and the red fluorescence of Evans blue albumin was traced under fluorescence microscope (*Steinwall & Klatzo* 1966).

Experimental group 2: Seven unilaterally X-ray-exposed rabbits received three dexamethasone injections, starting on the morning of the day before acute hypertension was induced as described above.

Controls: A. Two animals did not receive dexamethasone treatment, so that comparison could be made with earlier results of permeability lesions in hypertension by X-irradiated rabbits (*Blomstrand et al.* 1975). *B.* Six non-irradiated animals received dexamethasone in the same way as experimental group 2.

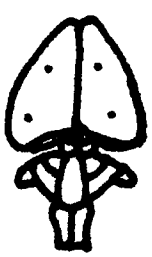
Results

The rise of the mean arterial blood pressure was 60–80 mmHg. There was no difference between the experimental groups and controls. As described in an earlier communication (*Blomstrand et al.* 1975), some scattered barrier lesions were seen in rabbits subjected to acute hypertension. Dexamethasone treatment 1 day before Aramine® injection did not significantly change the pattern of tracer extravasation in non-irradiated animals.

In agreement with the earlier investigation, unilateral X-irradiation induced increased vulnerability on the irradiated side.

When X-irradiation was preceded by dexamethasone injection and followed by daily steroid administration until induction of acute hypertension, no increase in vessel

X-ray irradiation + hypertension



X-ray irradiation + hypertension + dexamethasone group 1
X-ray irradiation + hypertension + dexamethasone group 2
No irradiation + hypertension + dexamethasone

Figure 1.

vulnerability was noticed on the irradiated side. A similar preventive effect of dexamethasone was also obtained when the drug was started only 24 h before Aramine® injection in X-irradiated animals. A schematic demonstration of the results is given in Figure 1. No increase of blood sugar occurred after dexamethasone treatment.

Discussion

In an earlier study (*Blomstrand et al.* 1975), we found an increased vulnerability of cerebral vessels to blood pressure after irradiation. It was suggested that irradiation weakened the vessel walls and made them more susceptible to mechanical damage. The fluorescence microscopical picture had some similarities to that seen when hypertension was induced on dilated vessels (*Johansson* 1974). In the present experiments, dexamethasone prevented this irradiation effect. The reason for the beneficial effect of dexamethasone on brain oedema is obscure, but at least part of the effect must thus be on the vascular level.

The mechanism for protein extravasation in these lesions is not yet known. To elucidate this problem, electronmicroscopical investigations are under progress. In blood pressure induced barrier lesions, the protein tracer peroxidase can be visualized perivascularly outside arterioles, capillaries and also some venules. Time sequence studies indicate that the tracer can pass through endothelial cells by channel-like structures and pinocytosis, and also between endothelial cells by opened junctional complexes (*Hansson et al.*, in press). One week after unilateral exposure to X-irradiation, marked morphological changes can be seen, especially in the endothelial cells, which show swelling and hypertrophia and also increased pinocytosis on the exposed side (*Hansson et al.*, to be published).

In clinical radiation treatment of brain tumours, it is a great problem to give a dose which is sufficiently high to destroy the tumour and yet sufficiently *low* not to get lesions in the normal brain tissue. It is important to reduce the frequency of lesions in the normal tissue as much as possible, without lowering the radiation dose to subtherapeutical levels.

Our studies on X-ray effects on hypertension-induced brain barrier lesions suggest that hypertension and labile blood pressure should be taken into account before starting radiation therapy of brain tumours. If such therapy is given, dexamethasone therapy may have beneficial effects in reducing the risk of hypertension-induced blood-brain barrier damage.

References

Blomstrand, C., B. Johansson & B. Rosengren (1975): Blood-brain barrier lesions in acute hypertension in rabbits after unilateral X-ray exposure of brain. Acta neuropath. (Berl.) *31*, 97–102.— Galicich, J. H. & L. A. French (1961): Use of dexamethasone in the treatment of cerebral edema resulting from brain tumors and brain surgery. Amer. Practit. Dig. Treat. *12*, 169–174.—Hansson, H. A., C. Blomstrand, B. Johansson & B. Rosengren: Ultrastructural studies on cerebrovascular permeability in acute hypertension after X-ray exposure. To be published.—Hansson, H. A., B. Johansson & C. Blomstrand: Electronmicroscopical studies on cerebrovascular permeability in acute hypertension. Acta neuropath. (Berl.), in press.—Johansson, B. (1974): Blood brain barrier dysfunction in acute arterial hypertension after papaverine-induced vasodilatation. Acta neurol scand. *50*, 573–580.—Lee, M. C., A. R. Mastri, A. G. Waltz & R. B. Loewenson (1974): Ineffectiveness

of dexamethasone for treatment of experimental cerebral infarction. Stroke 5, 216–218.—McGraw, C. P., D. F. Fleming & J. H. Spruil (1974): Effect of methylprednisolone on experimental cerebral infarction in the Mongolian gerbil. Stroke 5, 444–446.—Maxwell, R. E., D. M. Long & L. A. French (1971): The effects of glucosteroids on experimental cold-induced brain edema. Gross morphological alterations and vascular permeability changes. J. Neurosurg. 34, 477–486.—Reulen, H. J. & K. Schürmann (eds.) (1972): Steroids and Brain Edema. Springer-Verlag, Berlin, Heidelberg, New York.—Rovit, R. L. & R. Hagan (1968): Steroids and cerebral edema: the effects of glucocorticoids on abnormal capillary permeability following cerebral injury in cats. J. Neuropath. exp. Neurol. 27, 277–299.—Steinwall, O. & I. Klatzo (1966): Selective vulnerability of the blood-brain barrier in chemically induced lesions. J. Neuropath. exp. Neurol. 25, 542–559.

Received May 21, 1975.

Christian Blomstrand, M.D.
Department of Neurology
Sahlgren Hospital
S-41345 Göteborg, Sweden