

PROCEEDINGS OF THE ANAESTHETIC RESEARCH SOCIETY
LONDON MEETING AT KING'S COLLEGE HOSPITAL, MARCH 30, 1974

Abstracts of work completed and in progress

STUDIES OF THE THERAPEUTIC VALUE OF
PROCAINE AND LIGNOCAINE IN MALIGNANT
HYPERPYREXIA

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Procaine has been recommended for the treatment of established human malignant hyperpyrexia by many workers since Beldavs et al. (1971) reported on its first successful use. More recently it has been shown that procaine hydrochloride prevented and reversed muscle contracture in human hyperpyrexia-sensitive muscle in vitro (Ellis, 1973).

Procaine and lignocaine have different effects on the sarcoplasmic reticulum (SR) binding of calcium. Theoretically procaine which encourages calcium rebinding by the SR should be the drug of choice and lignocaine which liberates calcium from the SR contraindicated. A study was made of the effects of these drugs on a malignant hyperpyrexia model.

Strips of innervated rat diaphragm muscle which develop an increase in resting tension similar to human hyperpyrexia muscle were used (Ellis and Harriman, 1973). The muscle was immersed in a tissue bath containing Krebs' solution at 37°C which was gassed continuously with a 5% CO₂/95% O₂ mixture. Muscle tension was measured using an isometric beam incorporating silicon strain gauges. Measurements were made using 16 male Wistar rats both before and after treatment with procaine hydrochloride (0.5–2 mM) and lignocaine hydrochloride (0.5–2 mM).

Both lignocaine and procaine increased the halothane-induced increase in tension and no significant difference between these drugs was detected. These results suggest either that procaine and lignocaine could be equally effective in the treatment of malignant hyperpyrexia or that both drugs in certain circumstances could be dangerous.

Using human muscle taken by motor point biopsy from malignant hyperpyrexia susceptible patients it has been found that there is an unexplained variation in the response of the muscle to procaine when stressed by halothane. In 1 patient it was possible to demonstrate that procaine increased resting muscle tone in halothane treated muscle.

Although procaine usually produces a dose-dependent suppression of halothane induced rigor, the results suggest that procaine could potentiate the muscle abnormality in the hyperpyrexia patient. It is therefore suggested that more caution be exercised in the use of procaine in the treatment of malignant hyperpyrexia unless in vitro testing of the patient's muscle has demonstrated a beneficial effect.

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CHANGES IN INTRACRANIAL PRESSURE AND
SYSTEMIC ARTERIAL PRESSURE DURING THE
TERMINATION OF ANAESTHESIA

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Although changes in intracranial pressure (i.c.p.) and systemic arterial pressure (s.a.p.) have been documented during the induction of general anaesthesia and during the initial surgery in patients undergoing craniotomy (Shapiro et al., 1972), little attention has been paid to changes in these measurements during the conclusion of anaesthesia. It is generally held that following internal intracranial decompression, changes in i.c.p. are minimal in the immediate post-surgical phase.

The results from 13 patients are reported. A posterior fossa decompression had been performed in 7 patients, and the remainder underwent a supratentorial craniotomy for tumour or aneurysm. In all patients, controlled ventilation and moderate hypocapnia (Pa_{CO₂} approximately 30 mm Hg) were used during surgery and drainage of c.s.f. via the ventricular catheter had been employed to assist the surgical exposure; the intracranial tension was judged to be satisfactory by the surgeon at the time of closure. Both i.c.p. and s.a.p. were measured throughout the termination of anaesthesia, from the completion of surgery until the patient was considered to be sufficiently alert to be transferred from the operating theatre. Intracranial pressure was monitored using an intraventricular catheter and s.a.p. was measured from an indwelling catheter in the dorsalis pedis or radial artery. Both pressures were recorded using pressure transducers with an oscilloscopic display and chart recorder.

In the period of conversion from controlled to spontaneous ventilation, both i.c.p. and s.a.p. showed a significant increase (table I). Even when the patient was ready to leave the theatre, both measurements were still significantly increased from the values during controlled ventilation. During removal of the endotracheal tube and suction, spikes of i.c.p. up to 55 mm Hg were registered, but spikes of s.a.p. were less striking. The increases in i.c.p. and s.a.p. did not always coincide in individual patients, nor did they relate to the total duration of these manoeuvres.

The results show that although the intracranial contents may be quite slack at the time of surgical closure, intracranial hypertension and an increase in systemic arterial pressure may occur during the termination of anaesthesia.

Possible mechanisms for the increase in i.c.p. are the increase in Pa_{CO₂}, necessary to achieve spontaneous ventilation, and an increase in central venous pressure. Increased responsiveness to painful stimuli may contribute to the rise in s.a.p.

The implications of this study are threefold. Firstly, during surgical closure it may be necessary to achieve normocapnia to assess the efficacy of an internal decompression, and secondly, it may be beneficial to leave the

TABLE I. *Changes in intracranial pressure (i.c.p.) and systemic arterial pressure (s.a.p.) during the termination of anaesthesia in 13 patients. Mean values \pm SE.*

	I.c.p. (mm Hg)	S.a.p. (mm Hg)
Controlled ventilation	11.2 \pm 2.1	95.3 \pm 6.2
Spontaneous ventilation	21.6 \pm 2.6 (*P<0.01)	113.4 \pm 6.5 (*P<0.01)
Ready to leave theatre	19.9 \pm 3.5 (*P<0.05)	115.4 \pm 7.0 (*P<0.01)

* P value indicates significance of the difference from values during controlled ventilation.

ventricular catheter on free drainage during the conclusion of anaesthesia. Finally, patients who have not had the benefit of an intracranial decompression during their anaesthetic, such as those undergoing angiography, may, at the termination of anaesthesia, suffer elevations in i.c.p. and s.a.p. far in excess of those recorded in this study.

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EFFECT OF ANAESTHESIA ON DNA SYNTHESIS IN CHINESE HAMSTER FIBROBLASTS

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It is known that depression of the growth rate of mammalian cell lines is a general effect of clinical concentrations of anaesthetics. Previous studies of inhibition of DNA synthesis have been carried out by measuring uptake of ^3H thymidine, and reduction of uptake has been shown with phytohaemagglutinin-stimulated lymphocytes (Bruce, 1972; Cullen, Sample and Chretien, 1972), and rat hepatoma cells (Jackson, 1973). However, appreciable effects have been only observed when exposure to the anaesthetic had started some hours before the addition of ^3H thymidine. It was thus possible that the anaesthetic had prevented the entry of cells into the DNA synthetic phase (S) of the cycle. Therefore, we carried out studies on Chinese hamster fibroblasts (CH cells), designed to distinguish between effects in S phase and in the pre-synthetic phase (G1). We first demonstrated that halothane does, in fact, inhibit the growth rate of CH cells in a dose-dependent manner, within the clinical range of concentrations. We also found that there is no apparent arrest in metaphase caused by halothane, such as that which occurs in plant cells.

The second series of experiments consisted of the determination of the effect of halothane on the rate of ^3H thymidine uptake, and hence the extent of DNA synthesis, by treating the cells with halothane administered simultaneously with the ^3H thymidine. We believe that this method specifically indicates the effect on S phase. The observed inhibition was minimal: uptake was 83% of control value on exposure to 2% halothane in the gas phase.

The third series of experiments employed synchronized cultures of CH cells, prepared by collecting cells rounded up for mitosis. G1 normally extends for 3–5 hours after mitosis. Anaesthesia during G1 caused a delay in the onset of the increased rate of ^3H thymidine uptake which denotes the S phase, and this delay was equal in length of time to the duration of exposure to the anaesthetic.

This effect was seen with halothane concentrations down to 2%.

We conclude that some event or events in the pre-synthetic phase (G1) is sensitive to low concentrations of halothane, and this is probably an important factor limiting growth rate during exposure to anaesthetics.

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CO₂ RESPONSIVENESS OF THE CEREBRAL CIRCULATION DURING HALOTHANE-INDUCED HYPOTENSION IN THE BABOON

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The response of the cerebral circulation to changes in arterial Pco_2 during hypotension is of clinical importance, yet the only information available is based on experiments in dogs during haemorrhagic hypotension, which yielded different results during hypocapnia (Harper and Glass, 1965; Häggendal, Nilsson and Norbäck, 1969). We have studied CO_2 responsiveness in non-human primates (baboons) during hypotension induced with halothane.

Cerebral blood flow was measured by xenon-133 clearance and carotid electromagnetic flowmeter in 5 anaesthetized baboons. Flow changes in response to Pco_2 changes were expressed as percentages of the flow value at $\text{Pa}_{\text{CO}_2} = 40$ mm Hg. Control measurements were made during light anaesthesia and CO_2 was altered, both by varying the ventilation volume and by adding CO_2 to the inspired gases. Arterial pressure was then reduced by adjusting the inspired halothane concentration, and CO_2 responsiveness was tested again. Finally, all measurements were repeated after discontinuance of halothane and recovery of arterial pressure. Venous pressure in the superior sagittal sinus was recorded, and cerebral perfusion pressure calculated as arterial minus sagittal sinus pressure. Blood halothane was measured by gas chromatography (Allott, Steward and Mapleson, 1971).

At normal arterial pressure (mean pressure = $88 \pm \text{SD}$, 9 mm Hg; systolic pressure = $113 \pm \text{SD}$, 11 mm Hg) and cerebral perfusion pressure (mean $78 \pm \text{SD}$, 8 mm Hg) cerebral blood flow showed a linear relationship with arterial Pco_2 over the Pa_{CO_2} range 25–70 mm Hg. The equations for the regression lines are given in table I. From these it will be seen that carotid flow changed by 3.4% mm Hg⁻¹, grey matter flow by 4.0% mm Hg⁻¹, and mean cerebral blood flow by 3.9% mm Hg⁻¹. The mean cerebral venous halothane concentration was 6.5 ± 2.3 mg/100 ml.

During hypotension (mean arterial pressure = $44 \pm \text{SD}$, 9 mm Hg; systolic pressure = $58 \pm \text{SD}$, 11 mm Hg) and cerebral perfusion pressure = $32 \pm \text{SD}$, 7 mm Hg) there was no significant correlation between either per cent change in carotid blood flow or per cent change in cerebral blood flow (based on xenon clearance) and arterial Pco_2 , the latter being varied between 25 and 75 mm Hg. However, during hypotension there was a close relationship between perfusion pressure and per cent change in carotid blood flow ($y = 2.5x + 21$; $r = 0.867$; $n = 30$). The mean cerebral venous blood halothane concentration was $24.1 \pm \text{SD}$, 6.7 mg/100 ml.

In 1 animal studied at rather higher arterial and cerebral perfusion pressures (systolic pressure = 74–85 mm Hg;