AN EVALUATION OF PROCAINE IN THE TREATMENT OF MALIGNANT HYPERPYREXIA

I. M. C. CLARKE AND F. R. ELLIS

SUMMARY

Procaine has been advocated in the treatment of malignant hyperpyrexia, whereas lignocaine has been shown to worsen the condition. Using muscle from patients susceptible to malignant hyperpyrexia in vitro, it has been demonstrated that muscle contracture can occur with procaine on its own, and in one patient the halothane-induced contracture was potentiated by procaine. In other patients the concentration of procaine required to abolish the halothane-induced contracture was markedly above the clinical dose range. In a study of lignocaine and procaine on a caffeinated rat muscle (a suggested model for malignant hyperpyrexia) no significant difference was found in the ability of these local anaesthetics to alter resting tension of halothane-treated muscle; with both drugs the resting tension rose in a dose-related manner. The use of procaine as the drug of first choice in patients with malignant hyperpyrexia is challenged.

In 1971 Beldavs et al. reported the successful use of procainamide in the treatment of a patient with malignant hyperpyrexia. The patient had developed malignant hyperpyrexia (42°C, 112°F) with muscle rigidity towards the end of an anaesthetic during which thiopentone, nitrous oxide, halothane and suxamethonium had been given. Procainamide 700 mg was administered over a period of 8 min and the temperature fell to 36.7°C (98°F) in 19 min with abolition of the muscle rigidity. The rationale for the use of procainamide was based on the observations of Feinstein (1963) who found that procaine hydrochloride blocked the rigor produced in frog muscle by caffeine. The effect of procainamide on myotonia had prompted Geschwind and Simpson (1955) to suggest its use clinically in the relief of muscle rigidity. Harrison has shown that when Landrace pigs were given halothane to provoke malignant hyperpyrexia there was a reduction in mortality after pretreatment with procaine (Harrison, 1971). Using human hyperpyrexic muscle, Keaney and Ellis (1971) and Ellis (1973b) showed that pretreatment with procaine prevents and abolishes the contracture produced by halothane in vitro. We have confirmed these initial findings on eight muscle specimens taken from patients susceptible to malignant hyperpyrexia.

Since 1971 several patients have been given procaine or procainamide in the treatment of both the rigid and non-rigid varieties of malignant hyperpyrexia. Only three patients survived (Kalow et al., 1970; Maisel, Sessions and Miller, 1973; Barrett, 1973) and in one of these procaine seemed to have no effect on the rise in temperature. The non-survivors were given procaine or procainamide or lignocaine for their anti-arrhythmic actions rather than as a specific therapy for hyperpyrexia. Nevertheless, it has been suggested by several authors that a loading dose of up to 40 mg/kg procaine should be given even in the absence of muscle rigidity and this may be followed by an infusion of procaine 0.2 mg/kg/min. The negative inotropic effects of such large doses of procaine could be countered by isoprenaline.

For theoretical reasons procaine, which is known to accelerate calcium uptake into sarcoplasmic reticulum (Feinstein, 1963) and block the release of calcium from the sarcoplasmic reticulum by certain drugs (Thorpe and Seeman, 1973) should be more effective in malignant hyperpyrexia than lignocaine which enhances the leak of calcium from terminal sacs in the T-tubule system within the muscle. Yet lignocaine has been used in several patients with apparently beneficial results (Katz, 1970). We wish to report the results of in vitro investigations on both human muscle taken from patients susceptible to malignant hyperpyrexia, and animal muscle pretreated with caffeine. It has been shown...
(Harrison, 1973) that caffeinated rat muscle develops contracture with halothane in much the same way as muscle taken from patients susceptible to malignant hyperpyrexia treated with halothane (and most other inhalation anaesthetics) on its own (Keaney and Ellis, 1971; Ellis, 1973a; Ellis et al., 1971, 1972; Ellis and Harriman, 1973). Using a modification of the caffeine pretreated animal model, an experiment was devised to see if procaine and lignocaine differed in these actions on muscle.

METHODS

(i) The patients referred for investigation of susceptibility to malignant hyperpyrexia had a motor point muscle biopsy (Harriman, 1961) under modified general anaesthesia which avoided all the drugs known to induce malignant hyperpyrexia. The anaesthetic technique was developed especially for use in these patients and comprised intermittent thioptenone, fentanyl and nitrous oxide following diazepam premedication. Full temperature monitoring with cooling facilities was an obligatory part of the technique. Specimens of muscle were taken without stretching and placed in Krebs solution at room temperature for transport to the laboratory.

Strips of muscle 1 mm x 1 mm x 20 mm which included the motor nerve insertion were microdissected to remove non-viable tissue and attached by one end to the lower of two platinum stimulating electrodes in a tissue bath which was perfused with Krebs solution at 37°C, pH 7.4, and gassed with 5% carbon dioxide in 95% oxygen. The upper free end of the muscle was attached by silk and silver chain to an isometric beam transducer. The muscle was directly stimulated supramaximally every 2 sec for 1 msec using a Medelec TS2 nerve stimulator. The isometric beam assembly was moved up and down by means of a constant speed motor and the length/tension curves so produced were displayed together with superimposed muscle twitches on a Devices M2 chart recorder.

Anaesthetic vapours were administered to the muscle by passing the gassing mixture through a variety of temperature-compensated vaporizers (Cyprane Ltd) and other drugs were dissolved in the perfusate. The muscle was stretched to a predetermined length (approximately 130% of resting length), held for 1 min to allow stress relaxation to subside and then allowed to return to the resting length. The tension developed after 1 min at maximum length was measured.

(ii) Sixteen adult male Wistar rats weighing 150–250 g were sacrificed. The left hemidiaphragm was immediately dissected out, with the attached phrenic nerve and costal margin, and immersed in fresh Krebs solution. Radial strips of muscle similar in size to those used for the human studies were microdissected and treated in the same way as the human specimens Caffeine 1 mM/litre was added to the perfusate and halothane 1% v/v was vaporized by the gassing mixture in order to produce the model of activated hyperpyrexia muscle.

Following control measurements, procaine or lignocaine 0.5–2 mM/litre was substituted for the perfusate and repeat isometric contractions measured. Because it has been shown (Grist, Hall and Baum, 1973) that some preservatives in local anaesthetic solutions have an adverse effect on muscle metabolism and may cause uncoupling of oxidative phosphorylation, the local anaesthetic solutions were made up from pure crystals dissolved in caffeinated Krebs solution.

Procaine crystals were added to the plain (uncaffeinated) Krebs solution used in the human study and its effect on muscle tension measured.

RESULTS

(i) There was an increase in tension in one human muscle specimen studied when procaine was added to the perfusate in the absence of halothane (fig. 1). This patient is a member of a family known to be sensitive to malignant hyperpyrexia (Ellis et al., 1971).

In muscle from two other patients from malignant hyperpyrexia susceptible families, halothane produced contracture in vitro which procaine pretreatment was unable to prevent. Moreover, procaine would not abolish established contracture except in gross overdosage equivalent to many times the whole body lethal dose.

(ii) In the rat caffeinated muscle preparation both procaine and lignocaine caused an increase in tension, the magnitude of which was related to the dose of local anaesthetic used (fig. 2). The dose/response curves for the two drugs do not differ significantly (P>0.4).

DISCUSSION

It is important to study mammalian muscle at its normal temperature and pH since it is known that these are critical factors in determining the response of mammalian muscle to drugs. Bianchi and Bolton
Fig. 1. The effect of procaine on human malignant hyperpyrexia-susceptible muscle. The tension plotted on the vertical axis is the increase over a control tension of 1 gram. The upper curve represents the results for a specimen tested immediately after removal from the patient. The lower curve represents the results for a specimen tested some hours after removal.

(1967) found that procaine caused muscle contraction at pH 8.2 but not at pH 7.4. Isaacson, Hinkes and Taylor (1970) found that the effect of certain drugs, including procaine, on rat muscle was greatly modified by raising the temperature from 20°C to 37°C and Britt and Kalow (1973, personal communication) have been unable to demonstrate contraction produced by halothane alone in human hyperpyrexia-sensitive muscle working at 25°C, although this has been shown by Ellis at 37°C (Ellis et al., 1971) and later confirmed by others (Moulds and Denborough, 1974; Bradley and Murchison, 1972).

Harrison, using a preparation of rat rectus abdominis muscle, has shown that caffeine and halothane together will produce contracture (Harrison, 1973). This was produced by comparatively high concentrations of halothane (3% v/v) administered to a preparation maintained at a lower temperature than normal (30°C).

The present study has confirmed the findings of earlier workers that evidence from mammalian muscle obtained in experiments at 20-30°C may have no application to the same muscle at 37°C. More important in the clinical context of malignant hyperpyrexia, the studies suggest that procaine should no longer be regarded as the drug of first choice in the treatment of a hyperpyrexic episode. Although in two published case reports procaine has apparently been effective in reversing the hyperpyrexic process, in our experience it has failed to have any beneficial effect. The dose may have to be so large that circulatory depression becomes a...
serious problem. From our experimental results, it appears that a third group of patients exists in whom procaine may exacerbate the contracture.

Therefore, rather than advocate procaine therapy for every patient who develops malignant hyperpyrexia, it should be reserved for those in whom other measures such as intravenous dexamethasone (Ellis et al., 1974) have failed to prevent a progressive increase in temperature or increasing rigor. Ideally in vitro testing of muscle should be performed to see if procaine has a beneficial effect, although the speed of development of hyperpyrexia mitigates against the usefulness of this procedure in the emergency situation.

ACKNOWLEDGEMENTS
We thank Mrs S. Barlow for secretarial assistance and the Department of Medical Photography, United Leeds Hospitals for help in preparation of the figures. Cyprane Ltd provided a wide range of their vaporizers on extended loan. Financial help was given by The University of Leeds, and The Association of Anaesthetists of Great Britain and Ireland. I.M.CC is in receipt of a grant from the Special Endowment Fund of the United Leeds Hospitals who also provided some of the equipment.

REFERENCES


UNE EVALUATION DE LA PROCAINE DANS LE TRAITEMENT DE L'HYPERPYREXIE MALIGNE

RESUME
L'usage de la procaine a ete preferenc de traitement de l'hyperpyrexie maligne tandis que l'on a montre que la lignocaine aggrave la condition du patient. En utilisant in vitro du muscle provenant de patients predisposes a l'hyperpyrexie maligne, on a demontré que la contracture musculaire peut se produire avec la procaine seule, et dans un patient, la contracture induite par l'halothane a ete renforcee par la procaine. Dans d'autres patients, la concentration de procaine requisite pour supprimer la contracture induite par l'halothane etait nettement superieure a la plage de doses cliniques. Dans une etude de la lignocaine et de la procaine sur un muscle de rat calfeutre (modele suggere pour l'hyperpyrexie maligne), aucune difference appreciable n'a ete decouverte quant a l'apitude de ces anesthesiants locaux a modifier la tension au repos du muscle trait. a l'halothane. Avec les deux medicaments, la tension de repos a augmente d'une maniere liee a la dose. On met en doute la validite d'employer la procaine de preference a tout autre medicament pour les patients atteints d'hyperpyrexie maligne.

ÜBER DIE ANWENDUNG VON PROCAIN ZUR BEHANDLUNG VON MALIGNEN HYPERPYRIXEN

ZUSAMMENFASSUNG
Procain ist zur Behandlung von malignen Hyperpyrexien empfohlen worden, während nachgewiesen wurden, daß Lignocain eine Verschlechterung bewirkt. In-vitro-Ubersuchungen an Muskelparaten von für Hyperpyrexie anfälligen Patienten haben erwiesen, daß Procain auch bei alleiniger Anwendung Muskelkontraktionen hervorrufen kann, und bei einem Patienten wurde eine durch Halothan bewirkte Kontraktur durch Procain weiter verstärkt. Bei anderen Patienten lag die zur Behebung der Halothan-induzierten Kontraktur not-
PROCaine TREATMENT OF MALIGNANT HYPERPYREXIA

wendige Procainkonzentration erheblich über dem therapeu-tischen Dosierbereich. Bei einer an Koffein-behandel-ten Rattenmuskel (als einem möglichen Modell für die Hyperpyrexie) durchgeführten Untersuchung von Ligno-cain und Procain ergab sich für die Fähigkeit dieser beiden Lokalanästhetika die Ruhespannung im Halogen-behandelten muskel zu beeinflussen kein signifikant-er Unterschied; bei beiden Mitteln stieg die Ruhespannung der Dosis entsprechend an. Die Anwendung von Procain als Mittel der ersten Wahl bei malignen Hyperpyrexien wird in Frage gestellt.

VALORACION DE LA PROCAINA EN EL TRATAMIENTO DE LA Hiperpyrexia MALIGNA

SUMARIO
Se ha abogado por la procaina en el tratamiento de la hiperpyrexia maligna, ya que la lignocaina ha demostrado empeorar el estado del paciente. Utilizando músculo del paciente susceptible de hiperpyrexia maligna in vitro, se ha demostrado que la contracción muscular puede realizarse con procaina, por sí sola, y se aumentó en un paciente la contracción, por inducción con halotano, por medio de la procaina. En otros pacientes, la concentra-ción de procaina, requerida para suprimir la contracción por inducción con halotano, estuvo muy por debajo de la dosis clínica. En un estudio de lignocaina y procaina sobre un músculo cafeinado de rata (modelo sugerido para hiperpyrexia maligna) no se encontró ninguna diferen-cia significativa en la habilidad de estos anestésicos locales para alterar la tensión de descanso del músculo tratado con halotano; con ambas drogas la tensión de descanso resultó de acuerdo con la dosis. Se requiere el uso de procaina, como droga de primera elección, en pacientes con hiperpyrexia maligna.

OBSTETRIC ANAESTHETISTS ASSOCIATION

The Spring meeting will be held at the Leighton Hospital, Crewe, Cheshire, on Friday, March 21, 1975. Anyone wishing to present a paper or attend the meeting should contact Dr I. Mullock, Leighton Hospital, Crewe.

The Autumn meeting will be held in Bradford University, Bradford, Yorkshire, on Friday, September 12, 1975. Any person wishing to present a paper or attend this meeting may obtain details from Dr J. D. Holdsworth, Dewsbury Postgraduate Medical Centre, General Hospital, Dewsbury, W. Yorkshire, WF13 2LE.

Papers should be submitted before January 1 for the Spring meeting and before July 1 for the Autumn meeting.