RESPONSE OF MHS SWINE TO I.V. INFUSION OF LIGNOCAINE AND BUPIVACAINE

G. G. HARRISON AND D. F. MORRELL

SUMMARY

We report the negative response of MHS swine to i.v. infusions of lignocaine and bupivacaine yielding plasma concentrations which equal or exceed those reported in humans during extradural analgesia. It is concluded that local anaesthetic techniques using the amide-linked local anaesthetics administered in conventional dosage are safe to use in patients known to be genetically susceptible to malignant hyperthermia.

While it is accepted that the anaesthetic technique of lowest risk for the patient known to be genetically susceptible to malignant hyperthermia is some form of regional or local analgesia, strictures against the use of the amide-linked group of anaesthetic drugs (lignocaine and bupivacaine) are still voiced (Britt, 1973; Britt, Kwong and Endrenyi, 1977a; Relton, Britt and Steward, 1973; Strobel, 1977).

Such strictures are based on the work of Bianchi and others which demonstrated that lignocaine, in contrast to procaine and other ester-linked tertiary amine local anaesthetics, potentiated caffeine and caffeine/halothane induced contractures of muscle in vitro, enhancing also the oxygen uptake of such preparations (Bianchi and Boulton, 1967; Novotny and Bianchi, 1967; Bianchi, 1968; Strobel and Bianchi, 1971).

Clinical evidence cited in support of such strictures is scant and consists of "unpublished data" and "personal communication" reporting rare incidents of putative initiation of malignant hyperthermia by the administration of amide-linked anaesthetics to MHS individuals (Kalow et al., 1970; Britt, Kwong and Endrenyi, et al., 1977b).

In many hospitals today, the most readily available local anaesthetic drugs are usually members of the amide-linked group—lignocaine, mepivacaine and bupivacaine. This circumstance, and the fact that the concentration of lignocaine which produced potentiation of caffeine induced muscle rigor in vitro, was about 100-fold greater than the convulsive threshold in vivo in man (Foldes et al., 1960; Sasyniuk and Ogilvie, 1975), and was so greatly in excess of concentrations likely to be found systemically after conventional clinical use, stimulated us to examine the validity of these strictures against the use of such local anaesthetics in the MHS patient. We used the MHS Landrace pig as the experimental model.

We report here the response of MHS Landrace swine to the i.v. infusion of lignocaine and bupivacaine in doses which produced serum concentrations equal to and greater than those reported in humans following extradural and other major regional blocks or topical analgesia of the larynx.

METHODS

Four MHS Landrace swine, screened and identified as described previously (Harrison, 1977), were used in this investigation. The reactions of these animals were observed in response to the infusion of lignocaine on 10 occasions (two pigs three times, two pigs twice) and bupivacaine on eight occasions (four pigs twice). Subsequently, each pig was submitted to a confirmatory halothane challenge.

The plan for each infusion was as follows:

Anaesthesia was induced with thiopentone administered via an ear vein, the trachea was intubated and anaesthesia was maintained with nitrous oxide in oxygen administered by intermittent positive pressure ventilation using a Manley ventilator. When necessary, supplementary doses of thiopentone were administered. Body temperature was recorded from the probe of an Electric Universal Thermometer (TE3, ELLAB, Denmark) placed deep in the medial muscle mass of the thigh. A catheter was introduced into a jugular vein via a cut-down in the neck and advanced to the level of the right atrium. This catheter served for blood sampling and for the i.v.

G. G. Harrison, M.D., F.F.A.R.C.S. (Eng.); D. F. Morrell, M.B., Ch.B., F.F.A.(S.A.); Department of Anaesthetics, University of Cape Town, South Africa.

© Macmillan Journals Ltd 1980
administration of drugs. Blood samples (mixed venous blood) from this site were analysed for:

(1) Acid-base studies at 2, 5, 10, 15 and 30 min after local anaesthetic infusion (interpolation technique).

(2) Plasma concentrations of lignocaine/bupivacaine at 2, 5, 10, 15 and 30 min after infusion. Lignocaine and bupivacaine were assayed by the gas-liquid chromatographic method of Tucker (1970). A calibration curve with standard solutions was prepared from a blank specimen for each pig on each occasion. Using cyclizine hydrochloride as an internal standard and with quantitation by peak height ratios correlation coefficients were consistently greater than 0.998. (Pye Unicam GCV Chromatograph with dual FID and DP88 computing integrator using 2.1-m columns packed with 5% OV101.)

The test drugs, lignocaine and bupivacaine, were administered as follows: Lignocaine—initial dose 1.5 mg kg⁻¹ followed by infusion of 30 μg kg⁻¹ min⁻¹ in initial experiments, increased in later experiments to 2-3 mg kg⁻¹ and 120 μg kg⁻¹ min⁻¹. Bupivacaine—1 mg kg⁻¹ administered over 5-10 min.

In view of the importance of the free base form of the anaesthetic to its contracture-producing ability (Bianchi, 1968), we deliberately induced severe metabolic alkalosis in two test animals by infusions of sodium bicarbonate 4.2% in addition to the routine use of hyperventilation.

Criteria of the malignant hyperthermic syndrome sought included onset of muscle rigor resulting in characteristic extension of hind legs (Harrison, 1975); supraventricular tachycardia; rapid progressive increase in muscle temperature; and metabolic acidosis.

RESULTS
No sign of the onset of malignant hyperthermia syndrome was observed in any animal in response to the i.v. infusion of lignocaine or bupivacaine.

The plasma concentrations of lignocaine and bupivacaine assayed during infusion are recorded in figure 1. Mixed venous pH values during the majority of infusions (13) were in the range 7.4–7.5. The ranges 7.5–7.6 and 7.6–7.7 were noted in two infusions each, and 7.2–7.3 in one.

At the conclusion of the experiment all animals, when exposed to halothane, developed MHS syndrome to an extent which required treatment with dantrolene i.v. to ensure their survival.

DISCUSSION
When local anaesthetic techniques are used, with the notable exception of bilateral intercostal nerve blocks, the greatest plasma concentrations of local anaesthetic drugs are recorded in association with extradural anaesthesia.

In the case of lignocaine, concentrations from 2.4 μg ml⁻¹ (Tucker and Mather, 1975) to 4.5 μg ml⁻¹ (Covino and Vassallo, 1976) are reported. With bupivacaine, plasma concentrations reported range from the former authors’ report of 0.7 μg ml⁻¹ to 1.49 μg ml⁻¹ reported by Moore and others (1976). Exposure of MHS swine to such circulating concentrations and greater failed to evoke any untoward response. Our findings, considered with the lack of well-documented human cases of malignant hyperthermia provoked by lignocaine or bupivacaine, cast doubts on the validity of the strictures advocated on the use of the amide-linked group of local anaesthetic drugs in patients known to be susceptible to malignant hyperthermia, and suggest that these drugs may be safe when given in conventional clinical dosage.

ACKNOWLEDGEMENTS
MHS pigs were supplied by the J. S. Marais Laboratory of the Department of Surgery of the University of Cape Town and financial support came from Sterling Winthrop S.A. (Pty) Ltd. Assays were performed by Jeanne Meyer.

REFERENCES
LOCAL ANAESTHETICS IN MALIGNANT HYPERPYREXIA


REACTION DE PORCS SUSCEPTIBLES A L’HYPERPYREXIE MALIGNE A UNE INFUSION INTRAVEINEUSE DE LIGNOCAINE ET DE BUPIVACAINE

RESUME
Nou signalons dans cet article la réaction négative de porcs susceptibles à l’hyperpyrexie maligne (MHS), aux infusions de lignocaine et de bupivacaïne entraînant des concentrations dans le plasma équivalentes ou supérieures à celles signalées chez les humains pendant une analgésie extradurale. On en a conclu que les techniques d’anesthésie locale basées sur les agents anesthésiants locaux de la classe des amides peuvent être administrés sans danger et aux doses habituelles aux patients que l’on sait être génétiquement susceptibles à l’hyperthermie maligne.

REAKTION VON MHS-SCHWEINEN AUF INTRAVENÖSE INFUSION VON LIGNOCAIN UND BUPIVACAÏN

ZUSAMMENFASSUNG
Wir berichten über die negative Reaktion von MHS (anfällig auf maligne Hyperpyrexie)-Schweinen auf intravenöse Infusionen von Lignocain und Bupivacaïn in Plasmakonzentrationen, die diejenigen erreichen oder übertreffen, die bei Menschinen während extraduraler Analgesie gemeldet werden. Es wird geschlossen, dass Lokalanästhesiemethoden, bei denen amnestiilie lokale Betäubungsmittel in konventionellen Dosen verwendet werden, gefahrlos bei Patienten angewendet werden können, die genetisch auf maligne Hyperthermie anfällig sind.

RESPUESTA DE CHANCHOS CON HMS A INFUSIONES I.V. DE LIGNOCAINA Y DE BUPIVACAINA

SUMARIO
Informamos sobre la respuesta negativa del chancho con HMS a infusiones i.v. de lignocaina y de bupivacaïna que tuvieron por resultado concentraciones en el plasma iguales o mayores de las registradas en seres humanos durante la analgesia extradural. Se llega a la conclusión de que las técnicas de anestesia local mediante agentes anestésicos locales del grupo de las amidas administrados según dosis convencionales pueden usarse en toda seguridad en pacientes conocidos por ser susceptibles genéticamente a la hipertermia maligna.