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CONTROL OF THE MALIGNANT HYPERPYREXIC SYNDROME IN MHS SWINE BY DANTROLENE SODIUM

GAISFORD G. HARRISON

SUMMARY

Experiments are described which demonstrate that dantrolene sodium effectively terminates the syndrome of malignant hyperpyrexia induced in susceptible swine by exposure to halothane. Dantrolene is also shown to block initiation of the syndrome of malignant hyperpyrexia by halothane in MHS swine. Therapeutic use of this drug in patients with anaesthetic-induced malignant hyperpyrexia appears to be indicated.

Anaesthetic-induced malignant hyperpyrexia is a rare, often fatal syndrome affecting man and the pig, which results from a genetic intrinsic functional defect within the muscle fibre (Relton, Britt and Steward, 1973; Harrison, 1973b). Rigor of muscle is its predominant clinical feature.

In 1967, Snyder and associates reported the synthesis of a series of hydantoins which proved to have muscle relaxant properties. One of these, dantrolene sodium* was extensively investigated and its pharmacological effects were demonstrated to follow an action on the intrinsic mechanism of muscle contraction. In addition, it was shown to act only on skeletal muscle and to have no effect on cardiac muscle or smooth muscle (Ellis et al., 1973). Because of this, the effects of dantrolene sodium on the syndrome of malignant hyperpyrexia induced by halothane in malignant hyperpyrexia susceptible (MHS) swine were investigated.

METHOD

In this investigation, use was made of an experimental protocol previously described (Harrison, 1973a). In MHS swine selected by reaction to halothane prescreening and estimation of serum c.p.k. levels, monitoring of vital parameters was established under initial ketamine or ketamine/thiopentone anaesthesia, followed by endotracheal intubation and maintenance of anaesthesia with nitrous oxide and oxygen. IPPV was provided when required by a Blease Pulmoflator.

Monitoring included:

(1) E.c.g.

(2) Observation of rigor (see fig. 1).

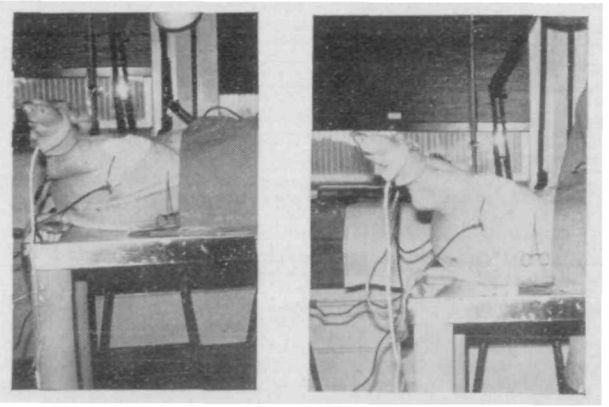

FIG. 1. MHS pig's hind legs before and after onset of rigor following halothane (note extension). The phenomenon may be recorded by attachment of the trotter by string over a pulley to a recording pen on a revolving drum. During rigor the muscle mass is palpably hard.

(3) Temperature measurement by means of a thermistor probe (Ellab, Denmark) inserted deep into the muscle mass of the thigh.

(4) Repeat sampling of mixed venous blood from a right atrial cannula.

Thereafter, the syndrome of malignant hyperpyrexia was initiated by the administration of halothane by IPPV commenced at a concentration of 2.5% and gradually reduced to 0.5% thereafter.

Once the hyperpyrexic syndrome was well established with marked muscle rigor, acidosis and an increase of temperature of 2°C or more, dantrolene sodium (0.5 mg/ml) was administered intravenously; a dosage of 1 mg/kg in early experiments was later increased to as much as 7–10 mg/kg.

The solubility of dantrolene is limited. The

*1-([5-(p-nitrophenyl) furfurylidene] amino) hydantoin sodium hydrate synthesized by Norwich Pharmacal Company Laboratories, New York.

GAISFORD G. HARRISON, M.D. (CAPE TOWN), F.F.A.R.C.S. (ENG.), Department of Anaesthetics, University of Cape Town, South Africa.

formulation used in these experiments was that described by Castellion (1973, personal communication):

dantrolene sodium 300 mg
mannitol 26.640 g
sodium hydroxide 48 mg
water to make 600 ml

Blood samples for acid-base, c.p.k. and potassium estimations were taken:

(1) Immediately before exposure to halothane.

(2) When the syndrome was established.

(3) After administration of dantrolene.

Eight such experiments were undertaken using 5 pigs, the experiment being performed three times in one pig, twice in another and once each in the remaining 3 pigs.

It must be appreciated that in this somewhat crude and empiric (though effective) intact animal experiment, judgement of the moment at which to commence treatment was difficult, and precise criteria as to the degree of temperature increase could not be adhered to. The rate at which reactor pigs develop the syndrome differs. While it was desired that the syndrome be well enough established in terms of muscle rigor and increase in temperature, to render any response to dantrolene unequivocal, care had to be taken not to jeopardize the entire experiment by risking sudden death of an animal from cardiac arrest resulting from the concomitant acidosis and hyperkalaemia. In some experiments, not only was the moment of commencing dantrolene dictated by the onset of cardiac arrhythmia, but in two animals "Isoptin" 5 mg (Iproveratril, Knoll, Germany) (shown in previous experiments to have no effect on the syndrome (Harrison, 1972, unpublished data)) was used to control this before the administration of dantrolene. Once well initiated, the syndrome is independent of the concentration of halothane, which appears to act as a trigger (Berman et al., 1970). In five experiments, halothane was discontinued 8–18 min before administration of dantrolene, the syndrome continuing unabated with further increases in temperature of from 0.5 to 1.9°C. In three experiments halothane was continued for 2–4 min after commencement of dantrolene. In neither event did this appear to affect the outcome.

The only ancillary treatment generally applied was the administration of sodium bicarbonate following the onset of rigor. Ambient temperature during these experiments was 21–22°C and with one exception active cooling was not used. In the exception, ice blocks were applied to an animal after the temperature had decreased from 43.8°C to 41°C. Ambient temperature on this day was 25°C.

Complementary to the therapeutic use of dantrolene, its ability to block initiation of the hyperpyrexic syndrome by halothane in MHS pigs was also investigated in two experiments (a week apart) on a single fast reactor pig. In these experiments, following establishment of monitoring under initial ketamine / nitrous oxide / oxygen anaesthesia as described, and treatment of the animal with dantrolene 3 mg/kg, the animal was exposed to halothane inhalation for 90 min. Commencing at 2.5%, the halothane concentration was reduced over 30 min to 1%, at which concentration it was maintained.

RESULTS

The results of these experiments with details of the duration of the malignant hyperpyrexic syndrome before treatment, the actual increase in body temperature, maximum temperature attained, dose of dantrolene and final outcome in terms of survival, are presented in table I. A temperature and events chart of one experiment, typical of all the experiments, is reproduced in figure 2.

In the established syndrome of malignant hyperpyrexia in susceptible pigs, the administration of dantrolene caused:

(1) Rapid loss of muscle rigor commencing within 5 min and usually complete within 20 min.

(2) Immediate cessation of the increase in deep muscle temperature followed by a rapid decrease.

(3) Termination of the progressive, inexorable acidosis characteristic of the syndrome (Harrison et al., 1969) rendering easy the buffering of acidosis developed until the dantrolene administration.

All pigs, except the first, used in the 8 experiments survived. This first pig, after showing a dramatic initial response to what, in the light of subsequent experience, proved to be too small a dose of dantrolene, suffered a recurrence of the syndrome with subsequent death (see table I).

Dantrolene pretreatment of an MHS pig effectively blocked initiation of the hyperpyrexic syndrome by halothane, allowing exposure of the animal to inhalation for 90 min with impunity. The time period of 90 min was chosen arbitrarily as being a period six times in excess of the previously tested "reaction" time of the pig used.

TABLE I

Pig No. and weight	Resting c.p.k. A units/ml at 25°C (normal 0-50)	MH duration before dantrolene (min)	Increase in temp. (°C)	Max. temp. (°C)	Dose of dantrolene (mg/kg)	Temp. decrease in first 20 min (°C)	Final temp. (°C)	Outcome
170 70 kg	364	36	3.2	40.1	1	0.6	42.0	Died
168 120 kg	720	14	2.1	38.5	1	1.9	36.7	Survived
168 125 kg	817	40	2.4	38.8	2.5	2.2	36.4	Survived
182 30 kg	4932	38	3.6	42.2	7	2.0	38.4	Survived
180 39 kg	1480	18	2.0	40.2	6	1.4	38.2	Survived
180 40 kg	1340	21	2.0	40.5	10	1.5	38.4	Survived
180 44 kg	1440	36	3.2	40.0	7	2.6	37.3	Survived
74 30 kg	348	30	3.8	42.8	10	1.8	38.0 Ice packs	Survived

Different weights recorded for the same pig used more than once reflect weight gain with time.

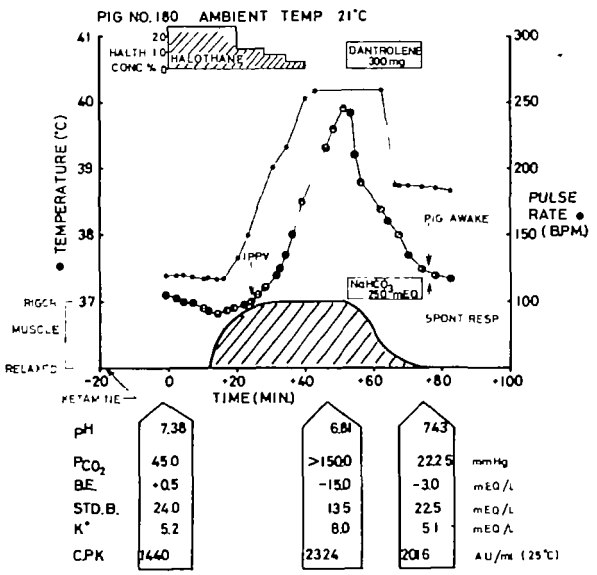

FIG. 2. Temperature (deep muscle) and events chart of typical experiment on MHS pig weighing 45 kg. Dantrolene administered as i.v. drip infusion for duration of square so marked. Biochemical values from mixed venous blood.

DISCUSSION

Untreated, the developed syndrome of malignant hyperpyrexia in pigs has a mortality rate of 100% (Harrison et al., 1969). While earlier work has demonstrated that it was possible to reverse the syndrome with procaine, especially if it was administered early enough (Harrison, 1971), the three out of five (60%) mortality for the established syndrome in pigs so treated described in this paper, has continued in our subsequent animal experiments. To date, procaine is the only drug that has been shown to have any effect on the established syndrome.

These experiments demonstrate that dantrolene has the property of relaxing the muscle rigor which characterizes malignant hyperpyrexia in the pig, and that concomitantly the excess heat and acid production cease. A survival rate of 100% was achieved in the last seven of eight experiments. In contrast to procaine, dantrolene has no effect on the myocardium, a factor which permits its use up to the limits of therapeutic effectiveness.

The pharmacology and toxicology of dantrolene have been extensively investigated in humans (Basmajian and Super, 1973; Chyatte and Birdsong, 1971; Chyatte, Birdsong and Bergman, 1971; Herman, Mayer and Newcombe, 1972) and it has been used extensively in the management of conditions characterized by muscle spasticity. The experiments reported here indicate that dantrolene should prove to be a most effective therapeutic agent in the treatment of malignant hyperpyrexia in humans.

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CONTROLE DU SYNDROME D'HYPERPYREXIE MALIGNE (DANS LES SUIDES MHS) AU MOYEN DU SODIUM DE DANTROLENE

RESUME

On décrit certaines expériences qui démontrent que le sodium de dantrolène met fin effectivement au syndrome d'hyperpyrexie maligne provoqué par l'exposition à l'halothane chez les suidés prédisposés. On montre également que le dantrolène bloque la manifestation initiale du syndrome d'hyperpyrexie maligne par l'halothane dans les suidés MHS. L'usage thérapeutique de ce remède semble indiqué pour les patients atteints d'hyperpyrexie maligne provoquée par un anesthésique.

BEKÄMPFUNG DES MALIGNEN HYPERPYREXIESYNDROMS (BEI MHS-SCHWEINEN) MIT DANTROLEN-NATRIUM

ZUSAMMENFASSUNG

Es werden Untersuchungen beschrieben, welche ergaben, daß Dantrolen-Natrium das bei empfänglichen Schweinen durch Halothan-Einwirkung hervorgerufene maligne Hyperpyrexiesyndrom wirksam kupiert. Außerdem konnte gezeigt werden, daß sich bei MHS-Schweinen die Auslösung eines malignen Hyperpyrexiesyndroms durch Halothan mit Dantrolen blockieren läßt. Das Mittel scheint sich also zur Behandlung von Narkose-bedingten malignen Hyperpyrexiesyndromen zu eignen.

CONTROL DE LOS SINDROMES DE HIPERPIREXIA MALIGNA (EN CERDOS CON SHM) POR SODIO DANTROLENICO

SUMARIO

Se describen los experimentos que demuestran que el sodio dantrolénico acaba eficazmente con el síndrome de hiperpirexia maligna, inducido en un cerdo, suceptible a ella, por exposición a halotano. Se muestra también que el Dantroleno bloquea la iniciación del síndrome de hiperpirexia maligna por halotano en cerdos con SHM. Parece ser apropiado el uso terapéutico de esta droga en pacientes con hiperpirexia maligna, de inducción anestésica.