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Dose-response relationship of atracurium besylate in the halothane-anaesthetised pig

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The dose response relationship for the intermediate-acting non-depolarising muscle relaxant, atracurium besylate in the pig was determined using evoked electromyography. An incremental dose technique was used in seven Large White/Landrace crossbred pigs anaesthetised with nitrous oxide and halothane. ED50 and ED95 were 510 ± 87 μg kg^{-1} and 1150 ± 270 μg kg^{-1}, respectively. Although these values may represent an overestimate, they provide a reasonable guideline for the use of atracurium by veterinary anaesthetists.

ATRACURIUM has previously been administered to malignant hyperpyrexia susceptible pigs (Lucke 1983, Morrell and Harrison 1986) and for the purpose of toxicity testing (Skarpa et al 1983). The neuromuscular-blocking potency of atracurium in the pig has not previously been determined. The objective of this study was to describe quantitatively the neuromuscular blocking effects of atracurium in the halothane-anaesthetised pig.

The study was approved by the Animal Welfare Committee of the University of Western Australia. Large White/Landrace crossbred pigs were obtained from the Western Australian Department of Agriculture Intensive Industrial Research Laboratories at Medina.

Seven Large White/Landrace crossbred pigs (five female and two male; age range seven to nine weeks; mean weight 31 kg, range 26 to 39 kg) were anaesthetised with halothane and nitrous oxide in oxygen (50 per cent) and endotracheal intubation was performed without the administration of muscle relaxants. An intravenous infusion of normal saline was given through a cannula placed in the ear. Controlled ventilation was adjusted to maintain an end-tidal carbon dioxide concentration of 30 to 40 mmHg. Anaesthesia was maintained with 50 per cent nitrous oxide in oxygen and halothane, 1 to 1·5 per cent (end-tidal concentration). A temperature monitoring probe (thermistor) was placed in the pharynx and an electrocardiogram monitored throughout the procedure.

Neuromuscular function was monitored electromyographically using the Datex NMT 221. The pig's right forelimb was firmly immobilised in partial extension and abduction and the sites for application of cutaneous electrodes were shaved, stroked with abrasive and thoroughly cleaned with alcohol. One stimulating electrode was placed 2 cm proximal to the midpoint of a line joining the medial epicondyle to the olecranon, and the second at a point 3 cm proximal to this. One sensing electrode was placed over the greatest prominence of the flexor muscles on the posteromedial aspect of the distal forelimb. The second sensing electrode was placed over the palmar aspect of the carpus. The fifth, neutral electrode was placed approximately midway between the sensing and stimulating electrodes. The ulnar nerve was stimulated in a train-of-four (TOF) pattern at 20 second intervals throughout the study period. This pattern of stimulation comprises four supramaximal square-wave stimuli each of 0·1 ms duration of 2 Hz. Having established a steady state of end-tidal halothane concentration of 1 to 1·5 per cent for 10 minutes, atracurium was administered in increments of 200 μg kg^{-1}. Following each increment, when three equal responses occurred, a further increment was administered until 95 per cent or greater depression of T1 (the first response following TOF stimulation) had occurred. Atracurium increments which produced complete ablation of T1 were not included in the calculation of the effective doses (ED).

For each pig, the log-dose response relationship was plotted and fitted to a sigmoid curve using computer-assisted, non-linear, least squares regression analysis. The ED50 and ED95 were calculated from the curve of best fit.

Upon completion of each study period, oropharyngeal temperatures ranged from 36·7 to 37·9°C. The times from administration of the first atracurium increment until the maximal response to the final increment ranged from nine to 14 minutes. A total of 32 points was used to construct the dose response and log-dose response relationships (Fig 1). ED50 and ED95 were 510 ± 87 μg kg^{-1} (mean ± SD) and 1150 ± 270 μg kg^{-1}, respectively.

The effective doses calculated in this study can be used to estimate an appropriate dose of atracurium for pigs anaesthetised with halothane. This will be particularly useful for procedures of short or intermediate duration.

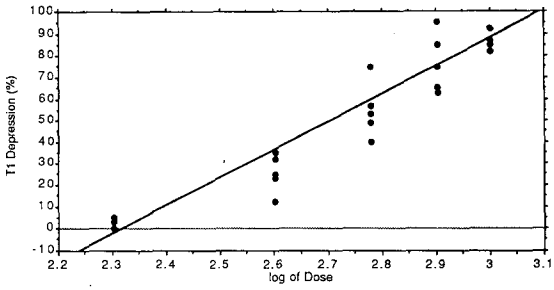

FIG 1: Log-dose response relationship of atracurium in the pig

For muscle relaxants with a duration of action of 45 to 60 minutes, the incremental dose technique is valid provided all increments are administered within a brief period (eg, 10 to 12 minutes) (Donlon et al 1980). The single bolus technique yielded significantly lower values for ED50 and ED95 of vecuronium in humans than the incremental dose technique (Gibson et al 1985). This difference probably arises because, with intermediate-acting agents, of which atracurium is one, recovery from initial increments has begun to occur while the later increments are being administered. Thus, the values obtained may be expected to overestimate the true ED50 and ED95. In fact subsequent administration of the calculated ED95 (1·1 mg kg^{-1}) has produced approximately 95 per cent twitch depression, suggesting that this overestimate is not great and that the values shown here will serve as useful guidelines for veterinary anaesthetists who wish to use atracurium in pigs.

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