ATRACURIUM BESYLATE, A NEW SKELETAL MUSCLE RELAXANT

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All non-depolarizing (competitive) neuromuscular blocking agents in present use have disadvantages. In particular, all exhibit vagal blockade and other cardiovascular effects in some degree (Hughes & Chapple, 1976) and all show a significant increase in the duration of neuromuscular blockade when excretion is inhibited by renal insufficiency (Wingard & Cook, 1971). Atracurium besylate is a potent, competitive neuromuscular blocking agent in anaesthetised cats, dogs, monkeys and man, and is substantially free from these disadvantages (Hughes & Chapple, 1980; Hunt, Hughes & Payne, 1980). It is one of a series of compounds designed to achieve ready fragmentation to inactive moieties *in vivo* by a combination of enzymic ester hydrolysis and facile base-catalysed degradation of its quaternary ammonium groups initiated at physiological pH (Stenlake *et al*, 1975, 1976, 1979).

Atracurium causes a non-depolarizing block of the isolated chick biventer-cervicis preparation without producing initial contracture. Dose-response curves for blockade of neuromuscular transmission of sciatic nerve-gastrocnemius muscle preparations and the cervical vagus and sympathetic nerves in anaesthetised monkeys show a wide separation between neuromuscular paralysing action and cardiovascular effects. Respiratory alkalosis (hyperventilation) with concomitant increase of plasma pH from 7.3 to 7.6 leads to a decrease in block and recovery time. Likewise, incubation of atracurium for 30 min at 37° with pH 7.4 buffer and human plasma respectively lead to falls of 50% and 75% respectively of neuromuscular blocking potency in the cat, consistent with inactivation by a combination of esterase hydrolysis and pH-dependent Hofmann elimination. In the absence of renal excretion, neuromuscular paralysing potency and the time-course of action of atracurium in anaesthetised cats was not significantly changed, whereas the potency of gallamine was increased about twofold and recovery considerably delayed.

Tracings from an anaesthetised patient recorded at fast paper speed after an intravenous dose of 0.25 mg/kg with simultaneous recording of tetanic and twitch responses, electrocardiogram, and arterial and central venous blood pressures and similar data from 28 anaesthetised patients demonstrate cardiovascular stability following atracurium at i.v. doses of 0.2, 0.3 and 0.6 mg/kg. Other tracings from anaesthetised patients show a consistent time-course of action following repetitive dosing, and reversal of blockade by neostigmine. The rate of recovery from peak tetanus following atracurium is more rapid than that from other competitive agents.

Hughes, R. & Chapple, D.J. (1976). Br. J. Anaesth., 48: 59-68

idem (1980). ibid, 52: 238P

Hunt, T.M., Hughes, R. & Payne, J.P. (1980) ibid, 52: 238-239P

Stenlake, J.B. et al (1975) British provisional patent application No. 50589/75

Stenlake, J.B. et al (1976) British provisional patent application No. 45028/76

Stenlake, J.B. et al (1979) U.S. Patent No. 4,179,507