AH 10407: A novel, short-acting, competitive neuromuscular blocking drug in animals and man

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It has been possible to obtain neuromuscular blocking drugs which are short-acting in animals, e.g. γ-oxalolaudonium (Brittain, Collier & D'Arcy, 1961), AH 8165 (Brittain & Tyers, 1973) and stercuronium (Hespe & Wieriks, 1971), but these drugs have a much more prolonged action in man (Blogg, Savege, Simpson, Ross & Simpson, 1973; Admiraal, 1973). A new compound, $1,1^1$-azobis [3-methyl-2-phenylbenzimidazolinium] dichloride, AH 10407 (Glover, Rowbottom & Bishop, 1973), has now been shown to be a short-acting, competitive, neuromuscular blocking drug in both animals and human beings. We wish to report the pharmacology of this compound and to discuss the basis for its brevity of action.

In the anaesthetized cat AH 10407, 0.4-1.6 mg kg^{-1} i.v., caused a dose-dependent neuromuscular block of the indirectly stimulated (1 Hz) tibialis muscle (28 ± 2.7 to 94 ± 4.2%) which lasted from 14-45 seconds. The onset of block following single doses was very rapid (5-10 sec). In addition, when AH 10407 was infused intravenously at 0.5 mg kg^{-1} min^{-1} for 1 h, recovery from the block (97%) was complete within 60 sec of stopping the infusion. The neuromuscular blocking action of AH 10407 was rapidly and completely reversed by neostigmine, 0.05 mg kg^{-1} i.v.

In the anaesthetized cotton-eared marmoset, a primate which closely resembles man regarding the duration of action of neuromuscular blocking drugs, AH 10407, 2 mg kg^{-1} i.v., caused a 95% block of tibialis muscle twitches (f = 1 Hz) which lasted for 3 minutes. After toxicity studies in several animal species AH 10407 was investigated for its neuromuscular blocking action in conscious human volunteers. Using the ulnar nerve-adductor pollicis muscle preparation of the 'isolated' forearm, AH 10407, 0.4 mg i.v., caused a 63% block of muscle twitches which recovered in 1.1 min after removal of the tourniquet.

AH 10407 is rapidly degraded in the presence of bicarbonate ions. For example, in Krebs solution 83 ± 2.5% of AH 10407 is degraded within 1.5 min at 37°C and in human blood 90 ± 3.1% is degraded within 1.5 minutes. In neutral and acidic solutions AH 10407 is relatively stable. Therefore, it is probable that the very short duration of action of AH 10407 is due to base-catalyzed chemical degradation brought about by a nucleophilic attack by bicarbonate ions and other basic ions on the benzimidazolinium nucleus.

Although the inherent instability of AH 10407 results in problems in its chemical development and pharmaceutical formulation, the concept of designing molecules that are susceptible to base-catalyzed degradation would make possible a neuromuscular blocking drug that is reliably short-acting in man.

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