PANCURONIUM AND HISTAMINE RELEASE

R.I. BODMAN

FROM THE TIME of its introduction into anaesthesia pancuronium was said not to release histamine. In a definitive review of the pharmacology of pancuronium¹ two references are quoted to support this view. One² does not, in fact, contain the evidence quoted and the second,³ a report to a conference, has not been traced in the literature. Since then attempts have been made to compare the histamine releasing effects of d-tubocurarine and pancuronium by measuring plasma histamine levels⁴ and by measuring airway resistance.⁵ These workers concluded that pancuronium does not release histamine; consequently, this supposed advantage has been used to promote the use of pancuronium in preference to d-tubocurarine. However, four cases of bronchospasm following pancuronium have recently been reported in the literature⁶⁻⁹ and a fifth may have been attributable to this drug, although the writer preferred to incriminate thiopentone.¹⁰

A classical method of detecting histamine release in man is by the production of skin wheals by intradermal injection; as Paton remarks "intradermal injection is a valuable test ... which offers the advantage that a human tissue is used." This study provides a comparison of skin wheals produced by pancuronium and d-tubocurarine in man.

METHOD

These skin tests were undertaken with the sanction of the ethical committees of The General Hospital, St. John's, and the Medical School of Memorial University of Newfoundland. Fifty patients gave their consent to the tests, which were carried out while they were awaiting major operations for which a relaxant drug was to be used.

Equipotent doses of d-tubocurarine and pancuronium, with regard to muscle relaxation, were

R.I. Bodman, M.B., Ch.B., F.F.A.R.C.S., F.R.C.P.(C), Department of Anaesthesia, St. John's General Hospital, St. John's, Newfoundland, A1A 1E5.

From the Department of Anaesthesia, Faculty of Medicine, Memorial University of Newfoundland.

assumed to be in the ratio of 5 to 1. The dose of d-tubocurarine used was 0.15 mg in 0.05 ml, as supplied by the manufacturer (Squibb) i.e. as 3 mg per ml. The pancuronium (Organon) was supplied in a 2 mg per ml solution; this was diluted with water to make 0.03 mg in 0.05 ml.

The intradermal injections were made with 25-gauge needles on the anterior surface of the forearms, about two inches below the skin crease at the elbow, one drug on either side. The wheals were measured when they reached their maximum size, at about ten minutes. The outline was traced on the skin with a ball-point pen; thin millimeter-squared paper was damped lightly with a spirit swab and applied to the wheal with an even pressure. The outline of the wheal was thus transferred to the paper and the squares were counted.

RESULTS

The mean age of the 50 subjects was 40.5 (± 16.5) years. The areas of the wheals produced by d-tubocurarine was 157.3 (± 47.4) mm² and by pancuronium was 88.1 (± 21.0) mm². The difference was significant: $P < 0.001$. Figure 1 illustrates these distributions.

DISCUSSION

Comroe and Dripps¹² were the first deliberately to inject curare intradermally. They stopped short of a quantitative assessment with the comment that "a sensitivity test for curare cannot be carried out by intracutaneous injection since 100 per cent of individuals tested developed wheals." In 1948, Bain, Hellier & Warin¹³ showed that the areas of wheals and flares produced by histamine itself given intradermally were proportional to the log of the dose injected. Grob, Lilienthal & Harvey¹⁴ measured the diameters of skin wheals and found that 0.135 mg d-tubocurarine produced the same sized wheal as 0.1 mg histamine. Bodman¹⁵ first used this method on a new relaxant, when comparing laudexium with d-tubocurarine.

No deliberate study of pancuronium with respect to skin wheals seems to have been made in

FIGURE 1 Areas of skin wheals produced by equipotent doses of d-tubocurarine and pancuronium.

man. Observers have contented themselves with remarks such as "no rash seen on the upper chest",¹⁶ no wheal formation seen "at the site of injection".¹⁷ Attempts have been made to measure plasma histamine levels⁴ without conclusive results: this is not surprising as even during asthmatic attacks plasma histamine is not raised.¹⁸

It would appear from the present findings that the claim that pancuronium did not release histamine was premature. Besides, four cases of bronchospasm following pancuronium have now been reported.⁶⁻⁹

Bain, *et al.*¹³ showed that skin wheals produced by histamine are dose related. Paton¹⁰ has made the point that "histamine release is the more readily produced the more rapid the injection". So far as the skin is concerned this is borne out by the clinical observation that when d-tubocurarine is injected directly into a vein in a concentration of 10 mg per ml (as in Britain) flushing of the skin of the head, neck and upper chest is often seen, whereas this phenomenon is rarely seen in North America where the usual procedure is to use a 3 mg per ml solution and to inject this into an intravenous line.

On the other hand the effect of d-tubocurarine on bronchial muscle is clearly not dose related; it has never been demonstrated that small doses do not cause bronchospasm while large doses always do. In fact, considering the popularity of the drug over 30 years, the incidence of bronchospasm must be very small, leading to the conclusion that it is a "sensitivity" phenomenon. Doubt is, in fact, being cast on the causal relationship of histamine and asthma¹⁷: first, antihistamines (H¹ blockers) do not ameliorate or prevent asthmatic attacks, although they are effective against histamine released in the skin: secondly, plasma histamine is not raised during acute asthmatic

attacks: a number of other autotoc substances have been proposed, such as SRS-A, prostaglandins and the kinins.¹⁹

SUMMARY

Both d-tubocurarine and pancuronium release histamine in the skin: both have been shown to cause bronchospasm after intravenous injection. It is unlikely that skin testing with either drug will detect an individual susceptibility to bronchospasm, except as a non-specific test for atopy.

RÉSUMÉ

Le pancuronium, tout comme la tubocurarine en injection intradermique amène une libération d'histamine locale; on a par ailleurs rapporté des épisodes de bronchospasme avec les deux agents. Il est improbable qu'un test intradermique avant administration de l'un ou de l'autre agent permette la détection d'une susceptibilité individuelle à développer un bronchospasme à la suite de leur injection intraveineuse.

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