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Concerning Toxicity Testing of Atracurium

To the Editor: — We read with interest the letter by Nigrovic and Koechel,[1] published in the June issue of *Anesthesiology,* suggesting the need for additional toxicity testing of our new surgical muscle relaxant, atracurium besylate (Tracrium® Injection). Although the authors' statements regarding potential toxicity of acrylates are of little relevance to the clinical use of atracrium, we wish to correct their statement that "the toxicologic aspects of acrylate formation following atracurium administration have not, to our knowledge, been reported."

Atracurium underwent extensive preclinical toxicity testing prior to marketing, as do all new drugs approved by the FDA, and the pharmacokinetics and metabolism of atracurium have been studied thoroughly.[2-4] Nigrovic and Koechel apparently were unaware of the 1983 report in the *British Journal of Anaesthesia,*[5] which presented an overview of the preclinical toxicity testing program for atracurium. This testing program demonstrated that the administration of atracurium besylate (and thus exposure to its physiologic breakdown products) in dosage regimens that exceed those likely to be used clinically is not associated with any significant toxicity.

Chronic dosing studies were conducted in the rat, dog, and monkey to evaluate possible effects of atracurium on behavior, body weight, ophthalmologic status, hematology, clinical chemistry, urinalysis, organ weights, gross pathology, and histopathology of all major organ systems.[5] Atracurium was administered intravenously or subcutaneously in regimens that exceed the usual clinical regimens in terms of dosage, frequency of administration, and total duration of exposure. In one study, dogs received more than 4 mg/kg atracurium that had been degraded to 50% labeled strength (dose based on full potency) and, therefore, contained a high proportion of breakdown products.* No significant toxicologic effects were found in these chronic dosing studies. The use of three species and two different routes of administration resulted in the exposure of animals to atracurium itself and its physiologic breakdown products under a wide range of circumstances. Since the pharmacokinetic profile for atracurium is very similar in these animal models to that observed in humans, the lack of toxicity in these studies suggests that atracurium would be unlikely to have serious toxic effects in humans.

Other studies were conducted to evaluate the local effects of atracurium. In studies designed to assess effects on blood and vascular tissue, there was no evidence for local toxicity.[5]

Likewise, there was no evidence for sensitization potential in studies in which guinea pigs were injected intradermally every other day for 20 days with a solution of atracurium and challenged two weeks later with a subsequent exposure to atracurium.*

Atracurium also was evaluated in studies designed to address potential toxicity associated with inhalation or prolonged contact with skin.* These were done to address potential safety during shipment according to the Department of Transportation and International Air Transport Association Guidelines. Due to the unique metabolism of atracurium, these studies address the potential toxicity of atracurium and its breakdown products, including acrylates. The results further show the relatively low level of toxicity of atracurium in animals.

In an inhalation toxicity study, male and female rats were exposed in an inhalation chamber for 4 consecutive hours to an environment containing aerosolized atracurium powder at a minimal concentration of 15.4 mg/l of air. There were no deaths, and the total results revealed atracurium to be not dangerous by inhalation exposure.

Acute dermal toxicity was evaluated in New Zealand white rabbits with doses of 200 mg/kg of both atracurium powder and the 10 mg/ml solution marketed for clinical use. The drug preparations were applied to shaved skin areas, with the areas then covered securely with occlusive bandages for 24 h. No signs of skin irritation or systemic toxicity were seen. Acute primary skin irritation studies also were conducted in New Zealand white rabbits with both the 10 mg/ml solution of atracurium and atracurium powder. No signs of irritation or systemic toxicity were observed in either study.

In addition to the studies described above, extensive clinical studies of the safety of atracurium in human surgical patients were conducted in support of the New Drug Application (NDA) for Tracrium®. In approximately 500 of 875 patients treated with atracurium, extensive presurgical and postsurgical physical examinations and evaluations of hematology, clinical chemistry, and urinalysis findings were conducted to assess

* Data on file, Burroughs Wellcome Co.

possible adverse effects of atracurium. No atracurium-related effects on these parameters were found. As indicated in our Tracrium® package insert, adverse reactions in these clinical studies were minimal and largely confined to histamine-related events that occurred predominantly at dosages beyond the recommended dosage range.

Tracrium® has been on the market since December 1982 in England and since December 1983 in the United States. An estimated 1,000,000 patients have received the drug. Continuing product surveillance has revealed an extremely low incidence of adverse reactions, none of which suggest any tissue toxicity associated with atracurium administration.

In summary, we feel that the preclinical testing and clinical experience to date have demonstrated that Tracrium® is a safe and effective neuromuscular blocking agent.

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Further Comments Regarding Drug Disposition in the Surgical Patient

To the Editor: — Discussions with colleagues concerning our recent editorial, "New Approaches to Assessment of Drug Disposition in the Surgical Patient,"[1] prompt us to clarify a fundamental point which is of educational interest.

In our editorial we stated, "Collectively, these studies suggest that anesthesiologists should consider that the doses of many drugs given to surgical patients may need to be changed on commencement of total parenteral nutrition. Drugs eliminated primarily by hepatic metabolism especially require dosage adjustment." On the basis of the study of Pantuck *et al.*,[2] a uniform change should not be made in the dose of all drugs eliminated primarily by hepatic metabolism. Our editorial emphasized that a uniform change in drug dosage could not be made because of large interindividual pharmacokinetic variations in surgical patients. Nevertheless, *intraindividual* variations are often small, generally an order of magnitude less than *interindividual* variations, thereby permitting in a given patient extremely sensitive application of either the antipyrine test or of sequential comparisons of elimination rates of other drugs. This approach enabled Pantuck *et al.*[2] to identify nutritional factors as one potential cause of the previously recognized[3] perioperative induction of drug metabolism. While one cannot characterize as changed or unchanged the rate of elimination of a drug added to therapy in a particular patient during or after surgery, Pantuck *et al.*[2] have alerted us to the possibility of altered disposition of certain drugs in some patients following commencement of parenteral nutrition. This should increase the vigilence of anesthesiologists under such conditions. While the antipyrine test was the method used to make this discovery, the antipyrine test has several limitations.[4] For example, there is the well-recognized inability to extrapolate closely from results with the antipyrine test to other drugs.[4] One important contribution of the test is the demonstration that a given condition often produces large interindividual differences in this inductive effect, as illustrated by the results of Pantuck *et al.*[2] and Duvaldestin *et al.*[3] Therefore, at the present time we recommend a highly individualized approach to drug dosage in all surgical patients. The study of Pantuck *et al.*[2] should alert us to