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INDOCIN IN RHEUMATOID ARTHRITIS

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Since its introduction in March of 1965, Indocin has enjoyed wide public acceptance as an anti-arthritic agent. Early pharmacologic studies had indicated an unprecedented potency when the drug was used to control inflammation in various animal models. It was hoped, at that time, that Indocin would have a high therapeutic ratio and thus offer a significant advantage over corticosteroids with their multipilicity of serious adverse reactions. Unfortunately Indocin has shown a similar propensity to cause a wide variety of serious and sometimes fatal reactions, and its clinical usefulness has been limited by its toxicity. This toxicity has been well documented and is now well-appeciated by the medical profession, and Indocin has taken its place along side aspirin and phenylbutazone as another useful agent in a group of poorly understood diseases not amenable to any definitive therapy.

At no time, however, was the actual efficacy of Indocin questioned. It was appreciated that the drug worked considerably better in acute inflammatory conditions like gout than in the chronic arthritides such as rheumatoid arthritis, but the drug was believed efficacious in the latter condition. Several new studies published in the first quarter of 1967 in major scientific and medical journals now dispute the usefulness of this drug in rheumatoid arthritis. Chief among them in an exhaustive clinical study carried out by the Cooperating Clinics Committee of the American Rheumatism Association in association with Dr. Donald Mainland, a well-known biostatistician. This exhaustive study involved 141 patients treated for a three-month period and required ten months to be completed. Indomethacin was compared in a double-blind fashion with a placebo, the patients being allowed free use of aspirin as needed. Although many different parameters were measured and studied by sophisticated statistical techniques, the authors were unable to find any statistically significant differences in those parameters between Indocin and the placebo medication.

In the same month, Donnelley et al. published a similar study in the British Medical Journal. The British authors used a double-blind crossover study comparing Indocin with a placebo, and they also were unable to establish any statistically significant difference between Indocin and placebo. In neither study were there any serious reactions to the medications.

In a third article by Pinals and Frank no differences was found between Indomethacin and aspirin in the treatment of rheumatoid arthritis. This study was a double-blind crossover type and was not as thorough or as well planned as the previous two studies. The authors arrived at the conclusion that Indocin and aspirin have no significantly different effect on the parameters measured which is justified by the results of the experiment, but they seem to have missed the obvious conclusion that no therapeutic effect was demonstrated for either of the medications. The measured parameter, while not varying significantly between the Indocin-treated group and the aspirin treated group, also did not vary significantly within each group at two weeks and four weeks. The lack of inclusion of base line data adds a further difficulty to the interpretation of this paper. In contrast to this study, however, the Mainland and the Donnelly studies were well-planned, well-controlled, and seemed to be products of rigorous, thoughtful research.

Indocin's potential toxicity would make its use in rheumatoid arthritis unacceptable if indeed it has no efficacy for this condition. Therefore it was deemed necessary to review the original studies establishing efficacy in this disease. A search of 100 volumes of the NDA revealed six acceptable controlled studies, five of them double-blind the other single-blind. All of these studies claimed efficacy for Indocin but they vary in quality. As a whole, they would seem to indicate efficacy in this condition; results are summarized in the table, below.

In comparing the old studies to the new ones, it is obvious the latter are better-controlled and use more sophisticated methods of evaluation. Because of the extremely variable nature of the disease and the consequent difficulty in evaluating modes of therapy, it is impossible to say that the new studies outweigh the old, particularly in view of the large mass of testimonial data indicating efficacy. While testimonial studies are not in themselves adequate to allow approval of a drug by the FDA, they certainly cannot be disregarded as meaningless when the ultimate usefulness of the drug and its success is determined by individual