

infection was studied extensively in mice, rats, and rabbits, both before and subsequent to the initiation of clinical trials.

In the area of bacterial infection, in investigations in mice and rats, 10 different bacterial pathogenic microorganisms were used and the drug was given at several dose levels and treatment schedules. In contrast to hydrocortisone, indomethacin produced no detrimental effects in any of the experimental infections, even when administered in amounts 80 to 330 times the threshold dose for anti-inflammatory activity.

In the area of viral infection, indomethacin neither increased nor decreased resistance, in mice, to infections induced by the influenza A, Columbia SK, or the Eastern Equine encephalomyelitis virus.

In contrast to the adrenal corticosteroids, indomethacin did not depress antibody formation, which is a defense mechanism of the body against infection. These findings undoubtedly accounted, in part, for the contrasting effects of indomethacin and hydrocortisone on experimental bacterial infections, as mentioned above.

Taking all observations into account, it was held to be most probable that indomethacin would have no effect, beneficial or detrimental, on infections in man.

The safety assessment of indomethacin in the laboratory has been the most extensive we have ever undertaken and has included acute, subacute, and chronic toxicity studies in mice, rats, guinea pigs, rabbits, cats, dogs, monkeys, domestic pigs, and chickens. Chronic toxicity studies were continued for 26, 52, and 129 weeks in dogs; 35, 57, and 80 weeks in rats; 18 weeks in monkeys; 22 weeks in rabbits; and 27 weeks in guinea pigs. Acute and subacute toxicity studies were conducted in mice, cats, domestic pigs, and chickens. Reproduction studies included two-generation tests in mice, the recommended two-litter study in rats, and an established pregnancy test in rabbits.

The only toxicity that could be clearly identified as a direct effect of indomethacin was the production of gastrointestinal lesions of the type reported in animals for aspirin, phenylbutazone, and the anti-inflammatory steroids. Where anti-inflammatory potency and gastrointestinal irritation could be tested in the same species, the therapeutic ratio was as favorable for indomethacin as for phenylbutazone or the steroids. This type of potential side effect of antiarthritic dosages of aspirin, phenylbutazone, and steroids is well known to the physician.

Of course, there were other side effects we could not foresee which have occurred in man, but they were primarily of the subjective, sensory type, such as headache and dizziness, which are not usually observed in animals, since animals cannot communicate with man.

In the interest of time, I should like simply to condense the rest to say that the publications from our laboratories clearly disclose the results of the extensive animal studies carried on in the preclinical evaluation of indomethacin. They have not been challenged, even in the face of intensive investigation of the compound by other scientists.

The details of these studies are found in an extensive monograph which was provided each investigator and the FDA before clinical studies were undertaken. Reports of animal data to FDA and investigators were updated regularly to reflect the findings of animal studies continuing after the preclinical phase had been completed and the human studies were underway.