Human Toxicology and DMSO

The Human Toxicology Of Dimethyl Sulfoxide

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INTRODUCTION

On November 11, 1965, research on DMSO in the United States came to an abrupt halt. A conference between the Food and Drug Administration and the pharmaceutical companies who were involved in the research was called because lens changes had been observed in a number of mammalian species. No changes ha been observed in man or any primates. The FDA and the pharmaceutical companies agreed, because there had been no pretreatment examinations of eyes and a large number of patients were under therapy, to discontinue the clinical studies: Somehow, at this time, DMSO gained a reputation of extreme toxicity, comparable to that of thalidomide and some other drugs that had previously run into major toxicology problems. Many of us in the pharmaceutical industry felt that this reputation was undeserved.

A refractive index change in the lens (not an opacity) had been observed after ? months at a dose of approximately 5 g/kg in dogs, rabbits, and pigs. No microscopic or chemical differences could be found between the lenses of the treated animals am the controls. In the affected animals, there appeared two distinct zones of different refraction. This could easily by observed with an ophthalmoscope and with the slit lamp. It appeared to be a dose-related effect, and it diminished as the dose was reduced. It is noteworthy that the effect was produced at 50 to l00 times the usual human therapeutic dose.

In November, 1965 there had been no cases of confirmed eye damage or significant complaints in the studies of any of the pharmaceutical firms. Pre-treatment examinations of eyes had not been performed. We all felt that to re-examine all the patients who had been under treatment at this stage would be fruitless exercise, because of the age of many of the patients and their preexisting eye problems. We elected, therefore, to check

certain long-term patients on high doses. Drs. Jacob and Rosenbaum, in Portland, Oregon, had 32 patients examined by ophthalmologists connected with the University of Oregon Medical School. These had been treated for from 3 to 19 months, at an average dose of 30 g DMSO per day. None of these showed any of the characteristic lens changes that had been seen in the animals. One patient in Seattle was thoroughly checked. He had by chance had a complete pretreatment examination performed by an ophthalmologist several months prior to his neck injury. He was 19 years old, and at the date of his post-treatment exam he had received 60 g DMSO per day for 20 months. His follow-up exam was completely negative. This included tonometry, visual field, refraction, and slit lamp examination.

Dr. Scherbel, at Cleveland Clinic, had under treatment 44 cases of scleroderma. Their treatment was still continued under the new FDA rules. Some of these patients had received as much as 3 g/kg per day. Some were treated for as long as 23 months. Many lens abnormalities were observed in this group of patients, but none of those characteristically observed in the DMSO-treated animals. Therefore, the results of the examination of scleroderma cases were somewhat inconclusive.

During 1966, the pharmaceutical companies continued to collect case reports and no real toxicity of any kind was being observed. Merck and Company gradually collected 17,000 cases. Syntex collected approximately 7,00G and E. R. Squibb and Sons around 3,000. Monkey studies continued both in Germany and in the United States. No lens changes were observed at 11 g/kg dermally and 5 g/kg orally per day after one year. We came to the conclusion that these lens changes were probably species-specific, and that the primate was probably much more resistant than other mammals.

In January, 1967, I was retained as a consultant at E. R. Squibb and Sons to develop a program to reestablish clinical research on DMSO. It was apparent that the first step, before the contemplated studies in acute trauma and acute inflammation, would be a thorough study in human toxicology. We needed to determine the real degree of toxicity of the compound. If the material was truly toxic, no company would want to subject patients to risk; but if it could be proved clean, the rather wide potential uses of DMSO would warrant such a toxicology study. The Food and Drug Administration at the same time had planned a short-term study to evaluate only the lens problem. They agreed after consultation with E. R. Squibb and Sons to include their study as part of a complete toxicology study.

The short-term study was conducted at the State Prison Hospital at Vacaville, California in October of 1967. The long-term study was conducted at the same institution from November 21, 1967 to February 20, 1968. The chief investigator was Charles Lebo, M.D. A large number of other physicians became involved in the project because of the