

SOUTHWESTERN NEWS

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UT SOUTHWESTERN RESEARCHERS USING ASTHMA DRUG TO IMPROVE LEUKEMIA TREATMENT FOR CHILDREN

DALLAS — April 6, 1995 — Dr. Barton Kamen says the best ideas for research are found at the bedside of patients.

Kamen, a professor of pediatrics and pharmacology, and his colleagues at UT Southwestern Medical Center at Dallas knew some of their young patients were having problems tolerating the drug methotrexate used to treat acute lymphocytic leukemia (ALL). Although complications from methotrexate's use have been well documented, it has been the standard treatment for ALL patients for more than 40 years. Some of the complications reported by the patients include nausea, vomiting, drowsiness and severe headaches.

Standard therapies (steroids and pain relievers, for example) to treat the side effects were not working. Those problems sent Kamen, the pharmacologist, to the lab. The dramatic results of his and his colleagues' research were published in a recent issue of the British medical journal *The Lancet*.

"The biochemical questions raised by the patients are quite interesting," Kamen explained. "We were excited to learn that rheumatologists, in their experience of using methotrexate to treat rheumatoid arthritis, might have some answers for us."

Methotrexate promotes the release of adenosine. Rheumatologists believe that the release of adenosine may produce the pain-relieving anti-inflammatory effect of methotrexate in arthritis patients. Based on that assumption, Kamen wondered if the release of adenosine as a central nervous system depressant produced the side effects his patients experienced after taking the methotrexate.

"The next step for us," Kamen explained, "was to see if we could use aminophylline (a drug commonly used to treat asthma) to displace the adenosine and eliminate or reduce the side effects produced by the methotrexate, especially since we found that the adenosine in the

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cerebrospinal fluid was increased in some patients after taking methotrexate."

The physicians administered aminophylline to the patients after they received their leukemia treatment. Four of the six patients who had complications from the methotrexate were completely symptom-free within half an hour of being treated with the aminophylline. The other two patients felt significantly better but still experienced some nausea.

"We were very excited with the results," Kamen said. "While we still are unsure what causes all the severe reactions to methotrexate, it is clear that adenosine is associated with some of the neurotoxic side effects felt by our patients. It is also equally clear that we may have found a productive way to treat those complications."

Kamen and his colleagues also reported that the aminophylline did not decrease the cancer-fighting effectiveness of the methotrexate.

Kamen is an American Cancer Society Clinical Research Professor and holds the Carl B. and Florence E. King Foundation Distinguished Chair in Pediatric Oncology Research at UT Southwestern. His colleagues on the project were Dr. Juan Carlos Bernini, fellow; Dr. Daniel W. Fort, assistant instructor; Dr. James C. Griener, senior research scientist; and Dr. William B. Chappell, faculty associate, all from UT Southwestern's Department of Pediatrics; and Dr. Bernard J. Kane, pharmacologist at Children's Medical Center of Dallas. The research was funded by the Children's Cancer Fund of Dallas and the American Cancer Society.

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