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Carcinoid Syndrome Control With a New Antiserotonin Agent

Case Reports

THE ROLE OF SEROTONIN IN DISEASE has rapidly assumed increasing importance in many physical and emotional disorders in recent years as evidenced by a voluminous medical and scientific literature on the subject which includes psychiatric and neurological disorders, hypertension, Raynaud's disease, carcinoid tumor syndrome, interaction with or antagonism to LSD, rheumatoid arthritis, eclampsia, migraine, gastrointestinal disorders (such as ulcers, colitis and dumping syndrome), carcinomas and such allergic disorders as asthma. Our particular interest has dealt with the role of serotonin in the carcinoid syndrome.[1, 2, 3]

In a number of pharmacological test preparations, SQ 10,643 (2'-(3-Dimethylaminopropylthio) cinnamanilide hydrocholoride) manifested potent antiserotonin activity. SQ 10,643 in low doses specifically inhibited serotonin's oxytocic effect on the rat's uterus in vitro as well as serotonin's bronchoconstrictor and vasopressor actions in anesthetized dogs. SQ 10,643 also inhibited LSD-induced hyperthermia in rabbits. This antiserotonin agent inhibited gross excitation in mice and gastric mucosal erosions in rats, induced by large doses of 5-OH tryptophan. SQ 10,643 also manifested moderate anti-anaphylactoid effects in dextran-induced edema in rats or moderate antiphlogistic effects in localized edema produced by serotonin, bardykinin or histamine. SQ 10,643 blocked the EEG slowing produced by 5-OH tryptophan in cats. In other test preparations, however, SQ 10,643 was less specific or inactive as an antagonist to the actions of serotonin or 5-OH tryptophan.[4, 5]

The effects of this antiserotonin drug have been studied in three patients with proven advanced carcinoid metastases and carcinoid syndrome and are herein reported.

CASE REPORTS

Case # 1. A 36-year-old woman was admitted to Barnes Hospital for study on February 22, 1965. She was known to have extensive liver metastases from carcinoid tumor discovered surgically in June of 1964. She had previously been studied for management of her carcinoid syndrome which consisted principally of diarrhea and severe flushing. On a course of 5-fluoro-tryptophan (a tryptophan analog) she had accomplished complete response with return to a normal, well formed stool after each meal and with disappearance of severe flushing. Following the studies of July 1964, the patient had received additional courses of orally administered 5-fluoro-tryptophan for recurrences of flushing and diarrhea, but had received no chemotherapy for months when she was returned to the hospital for the current study.

At the time of admission she was having five or six loose stools daily and one prominent flush daily, usually immediately after breakfast. These symptoms were present despite her use of opium and atropine capsules daily in an attempt to control the diarrhea. During the flush she was aware, as were other observers, that her face became quite red. During the study period she received no medication except 10 mgm. of SQ 10,643 every six hours starting on February 25. She gradually developed less severity of the flush and the redness of her face disappeared. At the time of her discharge on March 5 (eight days later) she was having four soft bowel movements daily, which she considered normal, and was having a mild flush without redness usually around mid-morning.

After discharge from the hospital she continued taking SQ 10,643 (10 mgm.) four times daily for 51 additional days, at which time (April 25) medication was discontinued. She remained symptomatically well until May 19, when she began having recurrence of flushes three times daily and loose watery stools six to ten times daily. At this time she was restarted on SQ 10,643, 10 mgm. four times daily, and by June 7 (eighteen days later) she was having no flushes and was having one to two small bowel movements without diarrhea after meals. She continued on the SQ 10,643 until September 17,

at which time she was having no flushing and no diarrhea and taking no additional medication.

During her hospitalization daily 5 HIAA urinary studies revealed no appreciable change in excretion. Her blood count, urinalysis and BUN studies revealed no changes. After discharge from the hospital periodic physical examination and laboratory studies revealed no aberrations and the patient remained symptom free. Periodic checks of FBS, BUN, creatinine, cholesterol, AG ratio, cephalin flocculation, hemoglobin, sed. rate, hematocrit, WBC and differential blood counts remained constantly normal. The patient had no symptomatic side effects from the drug and was extremely pleased with her relief from symptoms of the carcinoid syndrome.

Case # 2. A 58-year-old woman with proven carcinoid metastases and carcinoid syndrome was rehospitalized on January 12, 1965. She had previously been treated in October 1964 with a course of 5-fluoro-tryptophan for management of her carcinoid syndrome which consisted predominantly of flushing and diarrhea. Since that time she had had no flushing but had experienced diarrhea which she had been able to limit to three loose stools daily by using one to three tablets of Lomotil® daily.

In the hospital this patient was given no drugs except 10 mgm. of SQ 10,643 every six hours. She was maintained on this program until her discharge from the hospital on January 23. Blood counts, urinalysis, BSP, FBS and BUN were found to be normal on admission as well as at the termination of her hospitalization. Daily quantitative urinalysis for 5 HIAA revealed no significant variation.

The SQ 10,643 was well tolerated with no subjective or objective untoward effect. After one week of treatment, diarrhea subsided and did not require any anti-diarrheal drug previously used to reduce the stools to three loose movements daily. The serotonin activity was apparently "neutralized" since 5 HIAA in the urine was not reduced, in contrast to the results when the intracellular blocking agent (5-fluoro-tryptophan) had been utilized.

After discharge from the hospital the patient was put on a regimen of 10 mgm. of SQ 10,643 only three times daily and was unable to control her diarrhea without fortifying herself with three Lomotil® tablets daily. Even this combination did not relieve the severe pain which developed in her back and in the region of her liver as well as the cramps associated with her diarrhea. She was placed on complete abstinence from all drugs. Briefly and rapidly she developed ten to 12 loose watery stools daily with severe abdominal cramping, weight loss and sensation of serious illness with loss of ten pounds in approximately 14 days. During this time, because of pain following eating and nausea with vomiting, she was limiting herself finally to small amounts of liquids only.

On August 10, 1965, she was returned to a regimen of tryptophan analog (6-methyl-tryptophan, 200 mgm. every six hours) and SQ 10,643, 10 mgm. every six hours. Very promptly she began regaining weight and recovered from abdominal pain, diarrhea and flushing. Within three weeks she had regained eight pounds of weight, felt quite well and left her home in good spirits for a vacation cross-country from Oklahoma to Montana.

A report on the use of a new antiserotonin agent which has been effective in the control of the symptomatology due to the carcinoid syndrome. Three case reports are presented in detail, showing the efficacy of the new drug which was well tolerated in all instances. Doctor Costello is from the Department of Surgery, Washington University School of Medicine.

Case # 3. A 61-year-old woman was admitted to Barnes Hospital on March 15 and discharged on April 13, 1965. From an operation in July of 1963 she was known to have carcinoid of the ileum with lymph nodal and peritoneal metastases. She had been studied in October 1964 and was found to have complaints resulting principally from mental aberrations and severe generalized flushes, although she had never experienced diarrhea. Her pre-study urinary 5 HIAA varied from 27 to 47 mgm. % for four days (normal: less than 10). On the recent admission, she complained of epigastric burning which was relieved by food and almost continuous flushing which was very annoying to her. She was given 10 mgm. of SQ 10,643 every six hours for ten days, during which time her flushing became much milder and by her count varied from seven to 11 times daily. Her 5 HIAA excretion averaged 63.4 mgm. % daily.

For the following seven days a tryptophan analog, 5-fluoro-tryptophan, was added in the amount of 200 mgm. every six hours and her flushing became milder and varied from two to seven times daily while her 5 HIAA urinary excretion averaged 37.0 mgm. % daily. During the ensuing week, the 5-fluoro-tryptophan was increased to 200 mgm. every four hours and the patient was not able to count any definite episodes of flushing. Her 5 HIAA urinary excretion averaged 32.8 mgm. % daily which was 66% of her baseline pre-treatment average and approximately 50% of the average daily excretion while on SQ 10,643 alone.

During these observations the WBC, hemoglobin, hematocrit, blood sugar, BUN and urinalysis revealed no significant alteration, and the patient experienced no side effect or untoward reaction to the medications. She continued to receive 10 mgm. of SQ 10,643, alone every six hours until August 19, at which time she was having little, if any, flushing that she could recall. She volunteered that she had

not noticed any nausea which she had experienced frequently prior to medication.

Conclusion

A new antiserotonin agent, SQ 10,643 has been studied for its effect on the carcinoid syndrome in three proven cases of extensive carcinoid metastatic disease. Careful clinical and laboratory studies, originally in the hospital and subsequently outside the hospital, have been determined. In all three patients the symptoms were markedly or completely relieved and no evidence of clinical or laboratory toxicity to the chemical was apparent. While symptoms were controlled, the urinary excretion of 5 HIAA was not markedly influenced by the antiserotonin drug. In two patients, the addition of a tryptophan analog to the antiserotonin drug enhanced the clinical effectiveness; and in one patient, so studied, the urinary excretion of 5 HIAA was appreciably reduced. It is concluded on the basis of these three case studies that 5 HIAA is a potent antiserotonin agent in the management of the carcinoid syndrome, although it is not anticipated that the drug should have any effect on the growth of the tumor or the production of the serotonin.

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