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EFFECT OF SEROTONIN INHIBITORS ON CONNECTIVE TISSUE DISEASE

Experimental and Clinical Studies

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SEROTONIN, histamine, and norepinephrine are highly active biologic substances, widely distributed in the body, and capable of producing various pharmacologic actions. The primary function of serotonin is not known, but like norepinephrine, it is believed to play an important role as a mediator of nerve impulses in certain regions of the body. Serotonin has been implicated in allergic and anaphylactic reactions, as has histamine. The metabolic pathways for these amines are well established, but little is known about the basic intracellular events that control their synthesis, storage, release, destruction, and their interaction with various hormones. Experiments have been reported which indicate that serotonin may increase tissue permeability, may cause inflammation, may stimulate fibrous proliferation, may induce vasomotor reactions, and may provoke pain when injected into certain tissues. Local injection of serotonin into the rat's paw produces edema similar to that produced by histamine.[1] Serial injections of serotonin into the subcutaneous tissue of the rat result in local progressive collagenous and fibrous tissue proliferation within the dermis.[2] Injections of histamine into periarticular tissue of guinea pigs bring about inflammation and fibrosis of connective tissue.[3]

Certain clinical observations suggest also that these tissue mediators may affect the connective tissue system. The syndrome of malignant carcinoid, associated

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with increased amounts of serotonin and related substances, may be associated with fibroblastic proliferation of heart valves[4] and rheumatic manifestations, or with skin and connective tissue changes suggestive of scleroderma.[5] Recently we have observed a patient with malignant carcinoid in whom arthritis of the rheumatoid type developed. The accidental perivascular infiltration of norepinephrine occurring during an intravenous infusion of the catecholamine may result in severe tissue necrosis with sloughing and ulceration, followed by delayed healing, and in certain cases necessitates a skin graft of the ulcerated area. Myocardial necrosis has resulted from prolonged infusion of the amine.[6]

The increased frequency of shoulder-hand syndrome after myocardial infarction is well known, but the mechanism of action responsible for this complication is not clear. Recently it was reported that increased amounts of catecholamines occurred in blood, urine, and heart muscle of patients with myocardial infarction.[7,8]

Because these naturally occurring amines appear to be implicated in some unexplained manner in various connective tissue disorders, studies with drugs that are known experimentally to alter serotonin activity were performed in a group of patients with various connective tissue disorders.

Experiments on Serotonin and Histamine Sensitivity

It was previously reported[9] that certain patients with connective tissue diseases were unusually sensitive to small doses of serotonin and histamine injected intradermally, periarticularly, or intraarticularly, in comparison with control subjects. The exaggerated reaction to 0.1 mg. of serotonin injected into the dorsum of the hand resulted in pain, erythema, and swelling about the injection site, cyanosis of the fingers, and arthralgia, which persisted for several hours *(Fig. 1A and B).* Control subjects usually showed only mild erythema at the site of the injections and mild arthralgia that disappeared in approximately one-half hour. Injections of similar amounts of histamine also resulted in exaggerated reactions in the patients as compared to reactions in normal subjects, although these reactions were usually less severe than those following injections of serotonin. Intradermal injections of 0.01 mg. of norepinephrine caused local pallor, and constriction of small vessels in the skin.

We have observed that several drugs, to be described, inhibit serotonin activity in experimental animals. The inflammatory reaction resulting from the injection of 10 mg. per kilogram of body weight of serotonin into a polyvinyl sponge implanted subcutaneously in the rat is completely blocked by 1 mg. per kilogram of methysergide or cyproheptadine *(Fig. 2A, B, and C).*

These drugs were administered to patients with exaggerated serotonin reactions to determine whether or not the reactions could be inhibited. Cyanosis and erythema usually diminished rapidly in from 5 to 10 minutes after intravenous administration of the serotonin inhibitor (methysergide, from 3 to 5 mg., cyproheptadine, from 5 to 25 mg.). Other experiments indicated that the serotonin

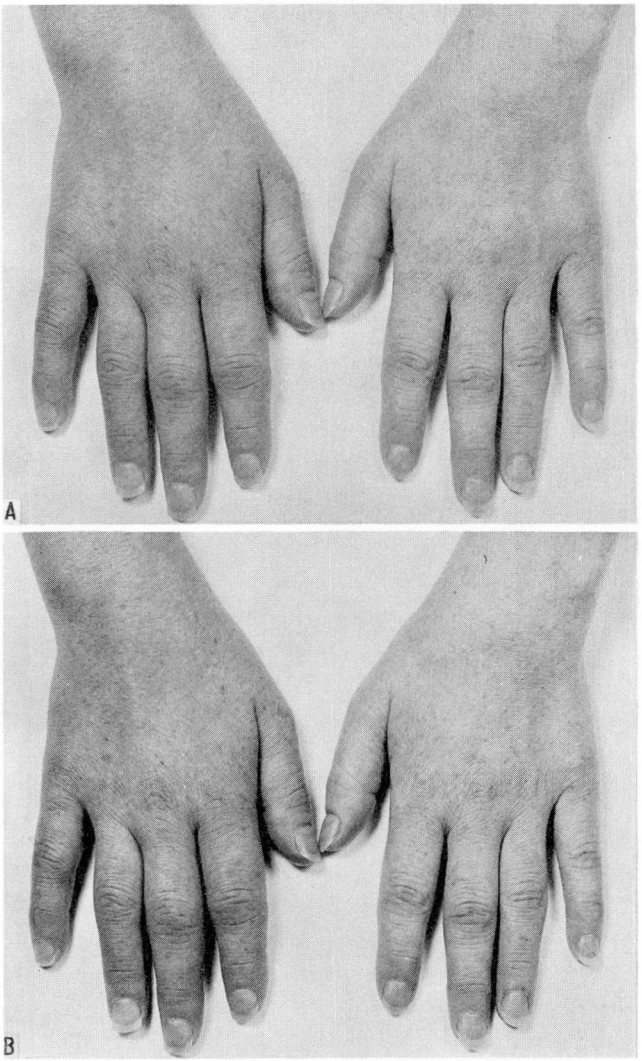
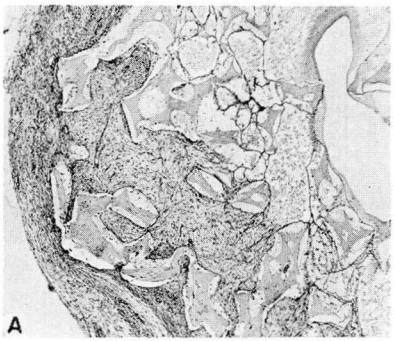
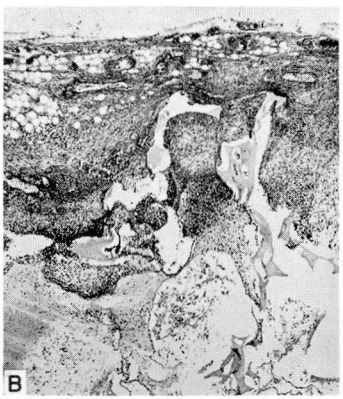


Fig. 1. A, Hands of housewife, aged 36 years, with rheumatoid arthritis of six-month duration. B, The same patient 10 minutes after periarticular injections of 0.1 mg. and 0.01 mg. of serotonin given about the proximal interphalangeal joints of the third finger of the right and left hands respectively. (From Scherbel, A. L., and Harrison, J. W.: Response to serotonin and its antagonists in patients with rheumatoid arthritis and related diseases. Angiology **10:** 29-33, 1959; courtesy of *Angiology.)*

reaction was neutralized when 0.1 mg. of a serotonin inhibitor was injected intradermally adjacent to the site of the serotonin reaction. These studies indicate that potent serotonin inhibitors, chemically unrelated, are capable of rapidly inactivat-





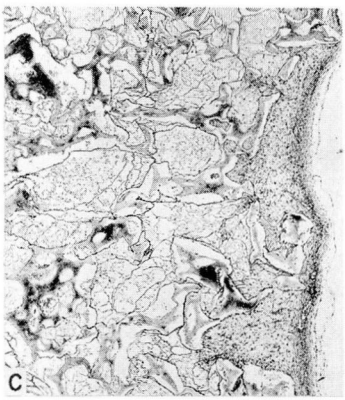
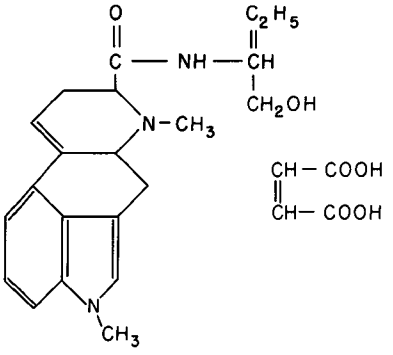


Fig. 2. A, Section of Ivalon sponge removed from control rat after seven days of local injections of 1 ml. physiologic saline solution daily. Fibroplasia extends centrally one eighth to one quarter the diameter of the sponge. Fibrinous exudate and inflammatory cells consisting of a few lymphocytes, plasma cells, and histiocytes are present centrally. Hematoxylin-eosin-methylene blue stains; X 50. B, Section of Ivalon sponge removed from control rat after seven days of injections of serotonin, 10 mg. per kilogram of body weight daily. An increased inflammatory reaction is present, but fibroplasia is not more extensive than that in the sponge in the control animal. Hemotoxylin-eosin-methylene blue stains; magnification X 50. C, Section of Ivalon sponge removed from rat after seven days of injections of 1 mg. per kilogram of body weight of methysergide daily, and 10 mg. per kilogram of serotonin daily. A decrease in the inflammatory reaction and fibrous tissue proliferation is seen as compared to the sponge in B, from the serotonin-injected rat. Hematoxylin-eosin-methylene blue stains; magnification X 40.

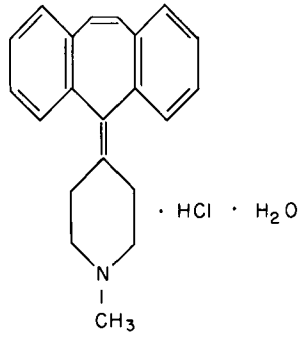
ing an exogenously induced serotonin reaction.

Drugs and Dosages

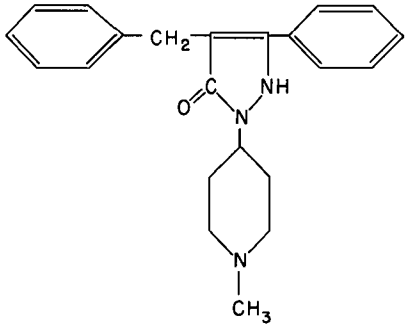
The structural formulas of the three drugs reported in this study, methysergide, cyproheptadine, and KB-95, are shown in *Figure 3.* Methysergide,* the methyl



Methysergide bimaleate



Cyproheptadine



KB-95

Fig. 3. Structural formulas of three drugs used in the study.

derivative of methylergonovine, is the most potent serotonin antagonist of the lysergic acid derivatives. In these studies intravenously administered doses ranged from 1 mg. to 15 mg. The doses administered into periarticular tissue, tendon sheaths, or joints ranged from 1 mg. to 3 mg. for each joint or tendon sheath. The total daily doses administered orally ranged from 4 mg. to 16 mg., the average being 2 mg. each three times daily. The total daily dose of methysergide did not exceed 16 mg. In 25 patients, it was orally administered continuously in daily doses of from 6 mg. to 8 mg. for 24 months or longer, with no evidence of toxicity.

**Sansert, Sandoz Pharmaceuticals.*

Cyproheptadine* has also been studied for almost three years. This drug has been reported to be effective in the treatment of certain allergic reactions, including some cases of bronchial asthma[10] and also experimental hypersensitivity vasculitis.[11] Experimentally, the serotonin inhibitory property is equal to that of methysergide; it also inhibits histamine. The doses administered intravenously ranged between 10 mg. and 50 mg. daily or an average of 30 mg. The total daily doses by mouth ranged between 4 mg. and 60 mg. in divided doses. The average dose for each adult has been 10 mg. three times daily. The doses administered parenterally into periarticular tissue, tendon sheaths, and joints ranged from 5 mg. to 10 mg., with the total daily dose not exceeding 60 mg. This drug has been administered continuously in doses ranging from 10 mg. to 30 mg. daily to 41 patients for two years or longer.

KB-95† is a relatively new serotonin inhibitor that has been studied clinically for nearly one year. It is one of the most potent serotonin inhibitors among the pyrazole derivatives. It can be tolerated in doses larger than those of the other serotonin inhibitors evaluated in connective tissue diseases. The daily dose given intravenously ranged from 100 mg. to 1,500 mg. for from five to seven days. The oral doses ranged between 75 mg. and 150 mg. each three to four times daily. Also, doses ranging between 140 mg. and 280 mg. each were injected intraarticularly.

Clinical Studies

Additional clinical studies were performed with serotonin inhibitors to determine whether or not they affected the clinical course of patients with various connective tissue disorders. The patients studied had rheumatoid disease, systemic sclerosis, systemic lupus erythematosus, dermatomyositis, or various types of vasculitis. Only patients with rheumatoid disease and systemic sclerosis are reported herein.

Rheumatoid disease. Serotonin inhibitors were administered to 162 patients with active rheumatoid disease during the last three years. Eighty-five selected patients, 49 females and 36 males from 6 to 71 years of age who had active disease for one year or longer and had previously been treated with sodium salicylate, a corticosteroid, a chloroquine derivative, or colloidal gold, with incomplete suppression of symptoms, have received one of the serotonin inhibitors daily for one year or longer.

All the serotonin inhibitors were most effective when administered intravenously or directly into or about joints or into tendon sheaths. Thirty-one adult patients received a serotonin inhibitor (diluted in 250 ml. of normal saline solution administered over a period of from 2 to 3 hours) intravenously for one or two weeks before receiving oral therapy. Ten patients received from 5 to 15 mg. of methysergide, 10 received from 25 to 50 mg. of cyproheptadine, and 11 received

Periactin, Merck Sharp & Dohme.
†*Sandoz Pharmaceuticals.*

from 100 to 1,500 mg. of KB-95, before receiving orally a serotonin inhibitor.

Throughout the study KB-95 was the most effective of the serotonin inhibitors administered, and methysergide was the least effective. The most common and consistent clinical effect observed after intravenous administration of a serotonin inhibitor was that pain began to diminish in from four to six hours after completion of the infusion. When daily infusions were administered, swelling and stiffness continued to lessen, and joint motion gradually increased each day. In about one-half of the patients who received intravenous medication, muscular weakness did not regress, and occasionally became more severe as treatment was continued. Increased weakness, sedation, and apathy usually appeared during the second week of treatment. Other effects occasionally observed after daily intravenous administration of a serotonin inhibitor included drowsiness, lightheadedness, and occasionally excitability with visual or aural hallucinations, especially when the drug was administered too rapidly or in great dosage.

The most significant response to these compounds occurred when they were injected directly into painful or inflamed joints or tendon sheaths. In most instances, pain subsided rapidly within a few minutes. The effect usually simulated that of a local anesthetic. Increase in joint motion was usually apparent. However, joint swelling and inflammation usually did not subside completely after a single intraarticular or periarticular injection. Joint pain and inflammation usually returned in from one to two days after the injection of methysergide or cyproheptadine. Improvement usually persisted for the longest time after the injection of KB-95; in some patients pain did not return for from 7 to 10 days.

The clinical response to oral administration of the serotonin inhibitors was usually not consistent, regardless of the serotonin inhibitor given. Only 11 of 60 patients who received KB-95 or cyproheptadine orally, responded rapidly to treatment, as manifested by relief of pain, and of joint swelling and tenderness within periods ranging from a few days to two weeks after treatment. This rapid response to a serotonin inhibitor did not occur with administration of methysergide. During this period of improvement no consistent change was apparent in the sedimentation rate, serum glycoprotein content, electrophoretic protein patterns, or titer of the latex fixation agglutination test. However, in three patients who responded rapidly to oral therapy, discontinuation of the drug after two months, and substitution of a placebo, resulted in recurrence of musculoskeletal manifestations in from 7 to 21 days after the placebo was first administered. Symptoms again subsided in from 6 to 14 days after the medication was readministered The other 49 patients in this group continued to have musculoskeletal manifestations three months after a serotonin inhibitor was first administered. Comparison of the 11 patients who improved symptomatically after the oral administration of a serotonin inhibitor with the 49 patients who did not improve, gave no consistent differences clinically or in laboratory studies before or after treatment was started.

Nearly one-half of the 49 patients who did not respond satisfactorily to a serotonin inhibitor actually had partial improvement in joint manifestations, but also increased muscular weakness, loss of energy, listlessness, and apathy developed. In 12 instances, psychomotor regression became apparent or increased in severity. Therefore, an amine oxidase inhibitor was administered in low dosage, and this usually resulted in mood elation and increased strength and energy. Moreover, further lessening of joint manifestations occurred in 30 of the 49 patients, when both an amine oxidase inhibitor and a serotonin inhibitor were administered simultaneously. Fifteen patients became free of joint pain and swelling, and noted only morning stiffness lasting approximately one-half hour or less.

The other 34 patients in this group of 49 continued to have generalized and persistent pain, aching, and morning stiffness in addition to intermittent swelling of various joints. Many of these patients who previously received large doses of a corticosteroid were considered to be addicted to the hormone. Therefore, administration of prednisone, in reduced dosage (2.5 mg. two to three times daily) was continued in the treatment program, with a serotonin inhibitor and an amine oxidase inhibitor. Those patients with withdrawal manifestations were also given corticotropin gel, 10 units each intramuscularly once weekly for from two to three months. Of the 34 patents, 30 improved slowly and irregularly but progressively during a six-month period. In each instance the amount of prednisone administered was at least 50 per cent less than the amount the patient had received previously. Disease fluctuations slowly diminished in severity and frequency and eventually disappeared almost completely in 24 patients during the subsequent 12 months of treatment.

No signs of toxicity were apparent in the liver, kidneys, or peripheral blood during this period of observation. In 8 of 34 patients receiving a corticosteroid, despite the low dosage, clinical manifestations indicative of mild hypersteroidism eventually appeared after six months of treatment. Excessive gain in weight, ranging between 10 and 20 pounds, without associated clinical manifestations of hypersteroidism, occurred in 10 patients during the first four months of treatment. Seven were receiving cyproheptadine, and three KB-95. Eight patients exhibited mild to moderate edema of the lower extremities, which was controlled by the simultaneous administration of a diuretic administered orally; six of these were taking cyproheptadine, and two, KB-95.

Thus, of 60 patients who received a serotonin inhibitor orally, 11 became free of all joint manifestations; 15 responded to a serotonin inhibitor plus an amine oxidase inhibitor; 34 patients received a serotonin inhibitor, an amine oxidase inhibitor, and a small dose of a corticosteroid. In this group of 34, 24 patients improved substantially despite a reduction in dosage of the hormone.

Primary systemic sclerosis. Serotonin inhibitors were administered for from one to three years to 15 patients (12 women and 3 men, aged from 24 to 59 years)

who had primary systemic sclerosis for from one to three years. Onset of the disease had occurred in from 1 to 10 years previously (average, 4.5 years). Thirteen patients had progressive disease. Tightness of the skin and subcutaneous tissue was present in 15; ischemic ulcers of the finger tips, interphalangeal joints or elbows in 8; subcutaneous calcinosis of the elbows or pelvic girdle in 3; cardiopulmonary involvement in 4; esophageal dilatation and shortening in 6; and hypertension, with a persistent diastolic pressure of more than 116 mg. of Hg in 2. Four patients were receiving digitalis because of cardiac failure.

Each of the serotonin inhibitors, KB-95, cyproheptadine, and methysergide, was administered in sequence for three-month intervals in 10 patients with primary systemic sclerosis. In 10 patients the drugs were administered first intravenously and later orally in dosages similar to those used in patients with rheumatoid arthritis. All the drugs were more effective when administered intravenously than when given by mouth. In general the results with methysergide were equivocal; KB-95 was the most beneficial in producing softening of the skin and subcutaneous tissue, and in the healing of ischemic ulcers. KB-95 also exerted a greater analgesic effect than did methysergide or cyproheptadine.

Softening of the skin and subcutaneous tissue appeared first, usually during the second week of intravenous therapy. This was observed over the proximal areas of the body and extremities, and later spread distally, but usually no farther than the metacarpal joints. In three patients with ischemic ulcers of the fingers, healing occurred during the first two weeks of therapy with cyproheptadine given intravenously in daily doses of 50 mg. each. In the three patients with subcutaneous calcinosis, there was definite softening and reduction of the size of the areas with intravenous therapy. Vital capacity improved slightly in one of four patients with pulmonary involvement, but clinical improvement in pulmonary reserve was not apparent. No change occurred in dysphagia in four patients. Weakness, lethargy, fatigability, and exhaustion occurred almost consistently in 8 of 10 patients receiving intravenous therapy daily for more than two weeks.

When serotonin inhibitors were administered orally as the sole therapeutic agent, improvement usually was neither consistent nor significant. Five of the eight patients noted softening and loosening of the skin, which was associated with increasing weakness and fatigability. Stimulation of appetite, weight gain, and fluid retention were other undesirable effects that occurred in four of the eight patients.

Comparison of the effects of the serotonin inhibitors during prolonged oral administration for three months or longer revealed that KB-95 was the most beneficial drug, when administered in doses of from 75 mg. to 150 mg. each three to four times daily. Two patients receiving KB-95 showed the greatest amount of softening of the skin resulting from oral treatment with a serotonin inhibitor. In doses that could be tolerated by the patients, methysergide caused the least clinical improvement.

As in most of the patients with rheumatoid disease, increased weakness, lethargy, apathy, and psychomotor regression appeared to a variable extent in 7 of 10 patients with primary systemic sclerosis within from one to two months after serotonin inhibitors were first administered. Thereafter, addition of small doses of an amine oxidase inhibitor rapidly resulted in increased strength, energy, and well-being. Moreover, a further increase in softening of the skin occurred in 3 of 10 patients who received both a serotonin inhibitor and an amine oxidase inhibitor. Corticosteroid therapy was maintained in 10 patients who had previously been so treated, but the doses never exceeded 2.5 mg. each of prednisone or its equivalent three times daily. In each instance, improvement, manifested by softening of the skin, healing of ulcers, and increased strength, was greater with combined therapy than it had been with larger doses of corticosteroids alone *(Fig. 4A and B).*

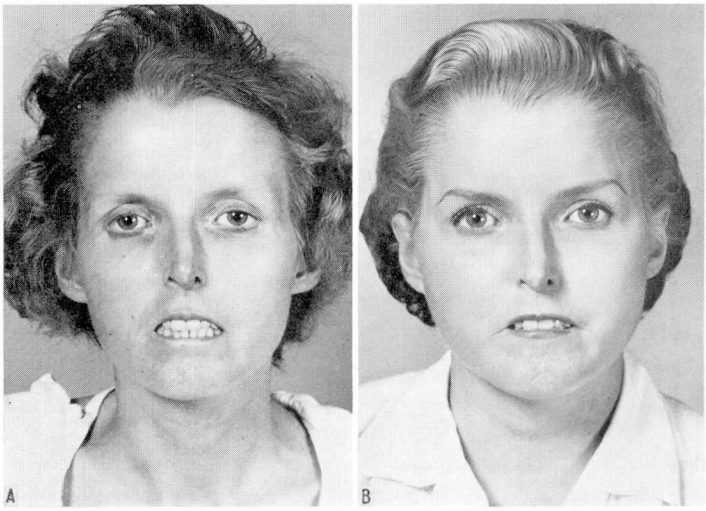


Fig. 4. Photos of a woman aged 34 years with primary systemic sclerosis of 3-year duration. A, Progressively downhill course. Previous treatment included oral methylprednisolone therapy chelation on two separate occasions, and chloroquine sulfate therapy. B, Patient four months after intravenous injections of serotonin inhibitor, and oral doses of amine oxidase inhibitor and methylprednisolone, 2 mg. each three times daily. (Corticosteroid therapy was reduced 50 per cent when treatment with the serotonin inhibitors was started.)

Three of four patients with progressive systemic sclerosis complicated by hypertension and cardiac failure died during the second and third months of therapy. In these patients, pre-existing progressive disease was not altered by treatment. Dyspnea in the fourth patient with cardiopulmonary involvement has not become more severe since treatment was started 12 months ago, but has improved slightly as shown by the patient's ability to increase physical activity 50 per cent without an increase in dyspnea, and a 10 per cent increase in vital capacity.

Spontaneous healing of ischemic ulcers occurred in two patients after an amine oxidase inhibitor was combined with the serotonin inhibitor. Local application of an amine oxidase inhibitor was necessary to induce healing in another patient. One patient with ischemic ulcers died without relief of symptoms or healing of ischemic ulcers on the finger tips, interphalangeal joints, and extensor surfaces of both elbows. In one patient two ulcers again developed on the finger tips after previous ulcers had healed, despite therapy with both a serotonin inhibitor and an amine oxidase inhibitor.

Clinical improvement after the administration of serotonin inhibitors in patients with systemic sclerosis was incomplete, but was considered of value in 11 of 15 patients because of softening of the skin and subcutaneous tissue, healing of ischemic ulcers, and lessening of vasomotor reactions. Increased strength and energy became more apparent, together with increased psychomotor activity when an amine oxidase inhibitor was administered simultaneously with a serotonin inhibitor. Corticosteroid therapy in small doses was administered to most patients, which appeared to increase the effectiveness of the other drugs. Relapses, which have occurred in all patients, have usually been mild and temporary. No significant improvement has been observed with respect to the cardiopulmonary, renal, or gastrointestinal manifestations.

Comment

A number of biologically active substances, which occur naturally in the body and are essential to normal function of certain regions of the nervous system, are capable experimentally of causing pain, inflammation, permeability of tissues, edema, necrosis, and fibrosis of the connective tissue system. However, there is no clinical evidence to indicate that a biochemical reaction involving serotonin, histamine, or the pyrocatecholamines occurs in diseases of connective tissue. Moreover, increased sensitivity to serotonin and histamine does not necessarily imply that these substances per se are responsible for the connective tissue changes in patients with connective tissue disorders. Nevertheless, the administration of serotonin inhibitors locally in inflamed and painful sites rapidly alleviates the connective tissue reaction.

This characteristic response to serotonin inhibitors is interesting, but the possibility that other unknown pharmacologic actions are responsible for clinical effects observed must be kept in mind. Studies to determine whether or not abnormal tissue binding of peripheral amines exists in patients with connective tissue diseases are now in progress. Preliminary studies suggest that drugs known experimentally to release tissue amines enhance the effect of serotonin inhibitors.

It is interesting that increased weakness, loss of energy, and psychomotor regression occurred in some patients simultaneously when a serotonin inhibitor was administered in doses effective in alleviating joint pain and inflammation. It

is conceivable that these drugs suppressed amine activity within the nervous system, as well as in the peripheral tissues, inasmuch as these symptoms were readily relieved by the simultaneous administration of an amine oxidase inhibitor. Stimulation of psychomotor activity associated with increased energy after the administration of amine oxidase inhibitors is thought to result from release of serotonin, norepinephrine, and related substances within the central nervous system.[12] If this concept is correct, it might explain why the simultaneous administration of an amine oxidase inhibitor alleviated the central effects of the serotonin inhibitors and resulted in further clinical improvement in many of these patients. In this connection, it seems significant that the currently available amine oxidase inhibitors, thought to increase the amount of serotonin and related substances within the central nervous system, do not appreciably increase the amount of serotonin in the peripheral tissues.[13] Therefore, aggravation of the inflammatory reaction in the connective tissue system would not be expected to occur from the administration of an amine oxidase inhibitor. Furthermore, experimental studies in animals and human volunteers indicate that the administration of amine oxidase inhibitors does not alter norepinephrine sensitivity of the peripheral tissues.[14-16] Hence the administration of a serotonin inhibitor simultaneously with an amine oxidase inhibitor would be expected to exert a more desirable, balanced effect than does either compound alone. This would result simultaneously in increased neurohumoral activity centrally, and diminished peripheral activity of the tissue mediators. Clinical observations suggest that both central and peripheral disease manifestations are lessened with use of this combination of drugs in some patients.

The great variation in clinical response to the oral administration of serotonin inhibitors, in contrast to intravenous administration, has not been adequately explained. Eleven of 60 patients with rheumatoid arthiritis showed excellent symptomatic improvement with KB-95 or cyproheptadine alone, and joint manifestations recurred when a placebo was substituted for the serotonin inhibitor. It is possible that differences in the tissue stores of certain amines, abnormal protein binding of these tissue mediators or some other biochemical abnormality may be responsible for the variation in clinical response in patients who allegedly have similar disease manifestations but who respond differently to equal amounts of the same drug. Preliminary studies with reserpine and related drugs thought to release tissue amines, suggest that this possibility is in need of further investigation.

The relationship of the tissue mediators to cortisone, while not clear, appears significant. It is thought that one of the functions of cortisone is to aid in the transport of tissue mediators. Our clinical studies indicate that corticosteroids, despite the small doses administered, were still necessary to induce desirable clinical effects in certain patients. It is not known whether a biochemical defect resulting in increased amines might lessen local cortisol activity at the connective tissue level, or that cortisol is necessary to release tissue amines, but it is apparent that the administration of serotonin inhibitors in certain instances increases

the antiinflammatory effect of the corticosteroids in some patients with connective tissue disorders, and permits a reduction in their administration. Hypersteroidism occurred in a few patients despite the low doses of corticosteroid administered. Thus the clinical response resulting from the administration of the serotonin inhibitor, may be an indirect effect that increases connective tissue sensitivity to cortisol.

It is not implied from these studies that biochemical abnormalities involving tissue mediators are causative factors of connective tissue disorders. Rather, it is suggested that unexplained metabolic alterations of tissue amines or increased binding activity between amines and certain proteins may exist as one of many complex biochemical changes occurring in connective tissue diseases, which in turn are capable of influencing disease manifestations within certain limits. This sensitivity to amine-releasing compounds appears to be greater in some patients than in others.

Serotonin inhibitors are not considered specific therapeutic agents for any of the connective tissue diseases, and produce only symptomatic improvement. Despite their rapid and complete blocking effect on exogenously administered serotonin, clinical response characterized by lessening of connective tissue inflammation is frequently delayed and incomplete unless treatment is supplemented with drugs that either increase amine activity within the central nervous system or release peripheral tissue amines. A similar response results from the addition of small doses of a corticosteroid. The over-all pharmacologic effects of these compounds is undoubtedly more complex than the simple inactivation of serotonin and related substances. Further study is necessary to determine whether unbinding or inactivation of tissue amines, or alterations of certain receptor sites are directly responsible for lessening of pain, inflammation, necrosis, edema, fibrous tissue proliferation, or whether alteration in pharmacologic action of these amines influences other unknown cellular enzymatic reactions responsible for connective tissue diseases.

Summary

Experimental studies have indicated that serotonin and related substances may increase tissue permeability, cause inflammation, stimulate fibrous proliferation, induce vasomotor reactions, and provoke pain when injected into certain tissues. Some clinical observations also suggest a possible relation of these amines to the connective tissue system. Serotonin inhibitors blocked the exaggerated intradermal response to serotonin in patients with connective tissue disease. When administered simultaneously with injections of serotonin in rats, the serotonin inhibitors resulted in diminution of the inflammatory reaction and fibrous proliferation observed when serotonin was given alone.

A study of the effects following the administration of methysergide, cyproheptadine, and KB-95 in patients with rheumatoid arthritis and primary systemic

sclerosis demonstrated that these serotonin inhibitors are most effective when administered intravenously or directly into the joints or tendon sheaths. KB-95 has been the most effective of the three drugs in doses tolerated by the patients. Among 60 patients with rheumatoid disease who received serotonin inhibitors by mouth only, 11 improved significantly with serotonin inhibitor alone; 15 responded to a serotonin inhibitor plus an amine oxidase inhibitor; 24 (of 34) patients who received a serotonin inhibitor, an amine oxidase inhibitor, and a small dose of corticosteroid improved considerably despite a reduction in dosage of the hormone. Clinical improvement after the administration of serotonin inhibitors to patients with primary systemic sclerosis occurred in 11 of 15 patients, with respect to softening of the skin and subcutaneous tissue, healing of ischemic ulcers, and lessening of vasomotor reactions.

These studies provide no basis for the assumption that a biochemical defect in amine metabolism is the primary causative factor in connective tissue diseases. Nevertheless, they indicate that drugs capable of altering amine metabolism may significantly influence disease manifestations in some patients. The results suggest that further investigation of the effects of amine inhibitors, and amine oxidase inhibitors, and tissue amine releasers, may contribute to the understanding of the many complex biochemical processes involved in numerous diseases.

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