RESPONSE TO SEROTONIN AND ITS ANTAGONISTS IN PATIENTS WITH RHEUMATOID ARTHRITIS AND RELATED DISEASES*†

ARTHUR L. SCHERBEL, M.D., AND JOHN W. HARRISON, M.D.

The primary role or roles of serotonin are not yet clearly defined although evidence is accumulating that it is involved in a variety of biologic processes. It is believed to play a part in central nervous system function.[1] Its effects on the cardiovascular system have been shown by various investigators to be complicated and highly variable. There are many theories as to what its main function there may be and the problem of whether serotonin may participate in regulation of blood flow by influencing neurogenic vasoconstriction is not known. We suspect that serotonin may also play a role in connective tissue disorders, although the mechanism of action is unknown.

Previously we reported that patients with rheumatoid arthritis and related diseases responded in an exaggerated fashion to intraarticular administration of serotonin.[2] In this report we wish to describe the response of periarticular and intradermal administration of serotonin and the effect of serotonin antagonists. A comparison between the reaction following serotonin and the reactions following histamine, norepinephrine, epinephrine, and acetylcholine is also described.

METHOD OF STUDY

Thirty-eight patients comprised the series for this study: 23 patients with active rheumatoid arthritis, 9 patients with active systemic lupus erythematosus, 4 patients with progressive systemic sclerosis, and 2 patients with acrosclerosis. In each patient serotonin and other amines together or separately were administered extravascularly and the reactions were observed and recorded. The reactions were compared with those that occurred in a control group of 16 normal persons who were given similar extravascular injections.

All periarticular injections were given adjacent to, and all intraarticular injections were given into, the proximal interphalangeal joints of the fingers. In patients with rheumatoid arthritis, uninvolved joints were injected. Intradermal injections were given into the dorsum of the hand midway between the metacarpophalangeal joints and the wrist at a point not overlying a vein.

Serotonin creatinine sulfate‡, hereafter termed serotonin, was diluted in physiologic saline solution so that the total volume of each injection was 0.1 ml. Six patients with active rheumatoid arthritis each were given an intraarticular injection of 0.01 mg of serotonin into a proximal interphalangeal joint. Six patients with active rheumatoid arthritis each were given an injection into the periarticular tissue of a proximal interphalangeal joint. Three patients in this group each were given 0.05 mg and three patients were each given 0.1 mg of serotonin. Eleven patients with active rheumatoid arthritis each were given an intradermal injection of 0.1 mg. of serotonin into the dorsum of the hand.

Three patients with systemic lupus erythematosus each were given a periarticular injection of 0.1 mg of serotonin and six patients each were given an intradermal injection of 0.1 mg of serotonin. Four patients with progressive systemic sclerosis and two patients with acrosclerosis each were given an intradermal injection of 0.1 mg of serotonin. In addition, the two latter patients each were given a periarticular injection of 0.1 mg of serotonin.

Three control subjects each were given 0.01 mg of intraarticular serotonin into a proximal interphalangeal joint. Three control subjects each were given 0.1 mg of serotonin into the periarticular tissue of a proximal interphalangeal joint. Ten control subjects each were given an intradermal injection of 0.1 mg of serotonin into the dorsum of the hand.

Histamine phosphate, hereafter termed histamine. Six patients with active rheumatoid arthri-

* Presented at Fourth Annual Meeting, American College of Angiology, June 21, 1958, San Francisco, California.

† From the Department of Rheumatic Diseases, The Cleveland Clinic Foundation and the Frank E. Bunts Educational Institute, Cleveland, Ohio.

‡ The serotonin creatinine sulfate used in this study was supplied through the courtesy of Joseph P. Webb, M.D., Medical Division, Upjohn Company, Kalamazoo, Michigan.

tis each were given 0.1 mg of histamine phosphate. Two patients of this group each were given a periarticular injection, and two patients each were given an intradermal injection. The reactions were compared with those following injections of serotonin.

Five control subjects each were given 0.1 mg of histamine. One member of this group was given an intraarticular injection, two each were given a periarticular injection, and two each were given an intradermal injection.

Serotonin and histamine. Three patients with active rheumatoid arthritis and one patient with acrosclerosis each were given a combined injection of 0.1 mg of serotonin and 0.1 mg of histamine into the periarticular tissues of a proximal interphalangeal joint of the hand. One control subject received a similar injection.

Norepinephrine or epinephrine. Two patients with active rheumatoid arthritis each were given an intradermal injection of 0.1 mg of norepinephrine and two patients each were given an intradermal injection of 0.1 mg of epinephrine into the dorsum of the hand. Three control subjects received similar injections.

Acetylcholine. Because of the possible relationship of acetylcholine to the amines under investigation, four patients with active rheumatoid arthritis each were given an intradermal injection of 0.1 mg of acetylcholine into the dorsum of the hand. Three control subjects received similar injections.

RESULTS

Response to serotonin. Twenty patients from the group of 23 patients with rheumatoid arthritis and 8 of the 9 patients with systemic lupus erythematosus demonstrated exaggerated responses to serotonin. Only one of the 16 control subjects developed a similar reaction. The reaction was characterized by diffuse pain and erythema; there was also swelling over the dorsum of the hand, which spread rapidly and occasionally extended proximally into the forearm and persisted for from 2 to 8 hr. The diffuse, irregular pattern suggested that the spread was occurring by way of venules and lymphatic channels. About 5 min. after the injection, cyanosis occurred in all of the fingers of the injected hand and became progressively more severe during the next 10 min. (fig. 1). Cyanosis persisted for periods ranging from 1 to 2 hr. The fingers became cold and occasionally were painful. Reactions were greater following periarticular or intradermal administration of serotonin in similar dosages as compared with intraarticular injections.

In patients who have progressive systemic sclerosis and acrosclerosis, the intradermally injected serotonin did not spread so rapidly or so extensively through the tissues as it did in patients who have active rheumatoid arthritis or systemic lupus erythematosus. In two patients the fingers did not become cyanotic unless a periarticular injection of serotonin was given, after which time only the involved finger became discolored. The cyanosis in these patients persisted 1 or 2 hr. and then slowly subsided. Erythema over the dorsum of the hand usually persisted from 2 to 6 hr.

In normal control subjects, only mild erythema and minimal swelling occurred regardless

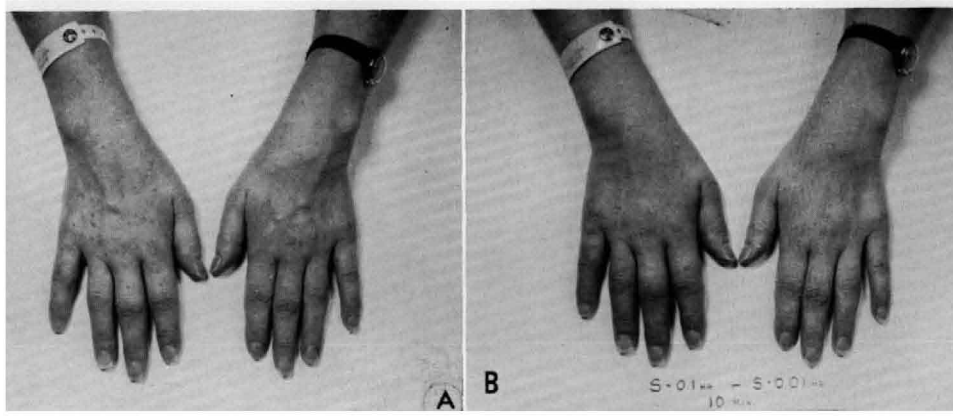

FIG. 1. (*A*) Hands of housewife, aged 36 years, with rheumatoid arthritis of six months' duration. (*B*) The same patient 10 minutes after periarticular injections of 0.1 mg and 0.01 mg of serotonin given into the proximal interphalangeal joints of the third finger of the right and left hands respectively.

of the manner or the site of the injection. Cyanosis of the fingers was not apparent except in one control girl, aged 18 years, who has since been found to have mild hypergammaglobulinemia and has noticed that her hands become cold when she is under emotional stress or in a cool environment. The mild reactions occurring in the control subjects usually disappeared within 30 min. Four of the control subjects described sensations of muscular aches and vague arthralgia persisting for several hours after the injections of serotonin.

In each of three control subjects an immediately given intradermal injection of 0.06 mg of epinephrine adjacent to the site of the serotonin injection produced an accentuation of the erythematous reaction interspersed with mottled areas of blanching which spread proximally to the shoulder. A similar accentuation was observed in two patients with active rheumatoid arthritis and in one patient with systemic lupus erythematosus. In the latter patients, the cyanosis of the fingers, which previously had occurred rapidly following the intradermal injection of serotonin, was slower in onset and less marked when epinephrine also was administered.

Response to histamine. The response to histamine injections in patients with active rheumatoid arthritis was characterized by erythema and swelling of a localized area over the dorsum of the hand. Slight cyanosis occurred only in one finger of one patient with active rheumatoid arthritis following intradermal injection of histamine. There was proximal interphalangeal joint inflammation present in the cyanotic finger prior to the injection. Erythema and swelling were comparable to that resulting from an injection of serotonin. Normal control subjects were observed to have only slight erythema and edema at the site of injection. Local itching was noted by all of the control subjects.

Response to histamine and serotonin. The combined periarticular administration of serotonin and histamine caused an exaggerated reaction that persisted longer than that due to the administration of either amine alone. The control subjects had only an exaggerated erythematous reaction with local itching and mild discomfort of the joints.

Response to acetylcholine. The intradermal administration of acetylcholine to four patients with active rheumatoid arthritis resulted in only mild erythema that was localized and did not spread. Cyanosis did not occur. There was no difference between the reaction of the patients with rheumatoid arthritis and the control subjects.

Response to epinephrine and norepinephrine. The intradermal injections of epinephrine and norepinephrine into four patients with active rheumatoid arthritis produced local pallor and constriction of small adjacent veins. Erythema, cyanosis, and swelling did not occur. The reactions in all four patients were similar and disappeared within 30 min. A less marked reaction occurred in four control subjects.

Response to serotonin antagonists. Ten patients with active rheumatoid arthritis who demonstrated exaggerated responses to intradermal or periarticular injections of 0.1 mg of serotonin each were given an intravenous injection of a known *in vitro* serotonin antagonist,[3, 4] 2-bromo-d-lysergic acid diethylamide (coded as BOL 148*). The dose usually was 2 mg given slowly during 5 min. In six patients cyanosis disappeared completely, and in four patients it diminished significantly (fig. 2).

Cyanosis disappeared first over the proximal portions of the fingers and then during the next 10 min. cleared distally in an irregular fashion. Frequently a mild amount of cyanosis persisted in the vascular beds within the periarticular tissues of the proximal interphalangeal joints. In the four patients showing incomplete clearing of cyanosis, there was a gradual return of cyanosis after about 30 min.; complete clearing occurred within the following 40 min. The only side effects noted from the intravenous administration of 2-bromo-d-lysergic acid diethylamide in dosages of 2 mg were mild sedative effects in all patients and transient nausea in four patients. Hallucinogenic and central stimulatory effects were not observed.

Two patients with rheumatoid arthritis and one with acrosclerosis who demonstrated an exaggerated response to intradermal serotonin in dosages of 0.1 mg each were given an intravenous injection of 1 mg of Hydergine† a mixture of three hydrogenated ergot alkaloids known to be a weak *in vitro* serotonin antagonist.[4, 5] In one patient the cyanosis disappeared completely, but in the other two patients it disappeared incompletely and then slowly reappeared. Two

* Supplied through the courtesy of R. Bircher, M.D., Medical Director, Sandoz Pharmaceuticals, Hanover, New Jersey.

† Manufactured by Sandoz Pharmaceuticals, Hanover, New Jersey.

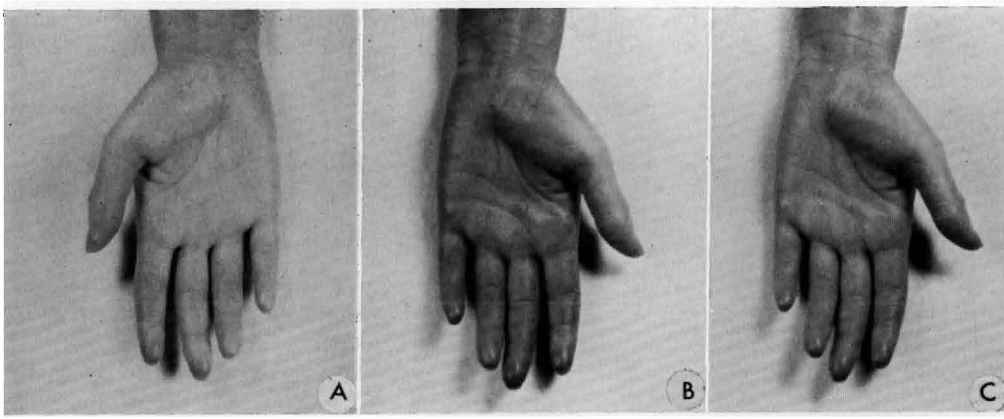

FIG. 2. (*A*) Hand of a housewife, aged 35 years, with acrosclerosis; (*B*) the same patient 10 minutes after an intradermal injection of 0.1 mg of serotonin into the dorsum of the hand; (*C*) the same patient 25 minutes after the intradermal injection of serotonin, and 10 minutes after an intravenous injection of 2 mg of 2-bromo-d-lysergic acid diethylamide.

patients with systemic lupus erythematosus and two patients with progressive systemic sclerosis who manifested cyanosis of the fingers following an intradermal injection of serotonin each were given 2 mg of Hydergine intravenously. In all four of these patients, cyanosis cleared slowly, beginning proximally and extending distally for periods of from 10 to 20 min.

COMMENT

The patients in this study who have rheumatoid arthritis, progressive systemic sclerosis, systemic lupus erythematosus, or acrosclerosis have demonstrated an exagerated reactivity to extravascular injections of serotonin and histamine. The reaction resulting from the injection of serotonin spread rapidly and persisted for prolonged periods. These patients appeared incapable of inhibiting or destroying serotonin when it was injected into extravascular tissue. Serotonin appeared to spread rapidly through the tissues by way of the venules and the lymphatic channels. Cyanosis was a characteristic part of the response to the injections of serotonin.

Reid[6] did not notice cyanosis after intradermal skin testing in human subjects using serotonin in his study of the local effects of this amine. Schneckloth, Page, Del Greco, and Corcoran[7] observed that intravenous injections of from 1.8 mg to 4.0 mg of serotonin provoked mild to intense flushes in normal subjects. Glover, Marshall, and Whelan[8] reported that intraarterial administration of 5-hydroxy-tryptamine into the brachial artery in normal subjects caused a fall in heat elimination and produced a vasoconstrictor response that could be abolished by the subsequent intraarterial or intravenous administration of 2-bromo-d-lysergic acid diethylamide or sodium salicylate. Heretofore, marked and persistent cyanosis was not reported as a feature of the reactions resulting from the administration of serotonin. It is known that only a small amount of serotonin is present in circulating blood, although it is possible that under certain conditions it may occur in special sites in amounts sufficient to cause increased vasoconstriction.

The weak systemic action that followed the intravenous administration of serotonin in relatively large doses in contrast to the potent local effect when it was administered into peripheral extravascular tissue appeared to be caused by a number of factors which include dilution of serotonin in the circulating blood, affiinity of the amine for platelets and red blood cells, and possibly the presence of an oxidase within the vascular walls preventing entrance of serotonin into the extravascular tissues.

This method of administering serotonin demonstrated an exaggerated vascular reaction *in vitro* in humans having certain rheumatic diseases, which was consistent in the small number of cases studied. Antagonism of this *in vivo* reaction was demonstrated by the administration either of 2-bromo-d-lysergic acid diethylamide or of Hydergine.

SUMMARY

1. Thirty-eight patients with active rheumatoid arthritis or related diseases exhibited exaggerated

responses manifested by pain, swelling, erythema, and cyanosis to extravascular administration of serotonin.

2. The reaction to histamine was characterized by itching, swelling, and erythema.

3. The reaction to epinephrine and norepinephrine was characterized by local pallor and venous constriction. Erythema, swelling, and cyanosis did not occur.

4. Acetycholine caused only mild, transient, local erythema.

5. The intravenous administration of a serotonin antagonist during the peak of the serotonin reaction rapidly diminished the intensity or reversed it completely.

Cleveland Clinic
Cleveland, Ohio

REFERENCES

1. Wooley, D. W., and Shaw, E.: Some neurophysiological aspects of serotonin. Brit. M. J., **2:** 122, 1954.
2. Scherbel, A. L.: The effect of Marsilid in patients having rheumatoid arthritis; the theoretical causal role of certain amine oxidases. J. Clin. & Exper. Psychopath., **19:** 118, 1958.
3. Sollero, L., Page, I. H., and Salmoiraghi, G. C.: Brom-lysergic acid diethylamide; highly potent serotonin antagonist. J. Pharmacol. & Exper. Therap., **117:** 10, 1956.
4. Gerletti, A., and Doepfner, W.: Comparative study on serotonin antagonism of amide derivatives of lysergic acid and of ergot alkaloids. J. Pharmacol. & Exper. Therap., **122:** 124, 1958.
5. Gaddum, J. H., Hameed, K. A., Hathway, D. E., and Stephens, F. F.: Quantitative studies of antagonists for 5-hydroxytryptamine. Quart. J. Exper. Physiol., **40:** 49, 1955.
6. Reid, G.: Circulatory effects of 5-hydroxytryptamine. J. Physiol., **118:** 435, 1952.
7. Schneckloth, R. D., Page, I. H., Del Greco, F., and Corcoran, A. C.: Effect of serotonin antagonists in normal subjects and patients with carcinoid tumors. Circulation, **16: 523,** 1957.
8. Glover, W. E., Marshall, R. J., and Whelan, R. E.: Antagonism of vascular effects of 5-hydroxytryptamine by BOL 148 and sodium salixylate in human subject. Brit. J. Pharmacol., **12:** 498, 1957.