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Vasopressor Effect of Synthetic 5-Hydroxytryptamine Creatinine Sulfate in Man.* (22500)

SERGIO I. MAGALINI,† MARIO STEFANINI, AND FRANCIS E. SMITH.

Saint Elizabeth's Hospital, Boston, and Department of Medicine, Tufts University Medical School.

Studies on hemostatic activity of 5-hydroxytryptamine creatinine sulfate (5-HT) indicated that administration of *small doses* of the drug into an antecubital vein caused often reflux of blood into the distal end of the plastic transfusion set, suggesting local elevation of venous pressure, while failing to affect systemic venous pressure(1). Further investigation was then undertaken on the fate of injected 5-HT(2) and on its effects on various circulatory districts.

Materials and methods. Fifty-two individuals, healthy or suffering from various diseases without elevation of venous pressure; one patient with ventricular septal defect and right to left shunt were studied. Seventy-nine experiments were performed. *Antecubital vein pressures* in one and or both arms were measured with saline manometers. On the injection side the pressure was obtained through the injection needle via a three-way stopcock during short, regular interruptions of the infusion. The system allowed separate infusions of drug or saline through the same needle. Brachial artery pressure was determined indirectly by means of aneroid sphygmomanometer. 5-*HT*§ in crystalline form was dissolved in physiological saline to prepare solutions of various strength.

Results. (a) *Local venopressor effect of 5-HT and its relation to concentration of drug.* (Fig. 1). Saline solution was first injected intravenously at a speed of 3 ml/min. for 5 minutes, without effect on the local or contralateral arm vein pressure. By different orientation of the stopcock, 3 ml/min. of 5-HT solutions of various strength were then administered for 5 minutes in 3 different sets of experiments. Injection of saline was now resumed for 15 minutes. Dose of 0.15 γ/5′ 5-HT caused negligible venopressor effect; 1.5 γ/5′ induced significant elevation of local venous pressure, lasting at least 5 minutes after the end of the infusion; a 10-fold dose (15 γ/5′) determined more pronounced and sustained response. There was no *systemic* venopressor response when a total amount of 45 γ were injected in 15 subjects (15 γ/5).

(b) *Effect of repeated or continued intravenous administration of 5-HT on local venous pressure.* Repeated intravenous infusions of 5-HT (1.5 γ/5 minutes) were given; saline solution was administered for 15 minutes between injections (Fig. 2) Venopressor response to 5-HT was progressively more pronounced as injections were repeated. Local, severe pain prevented continuation of the procedure for more than 3 times in succession. It is then not known whether decrease in local venopressor effect might, as observed in dogs

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† Damon Runyon Cancer Research Fellow.

‡ Established Investigator, Am. Heart Assn.

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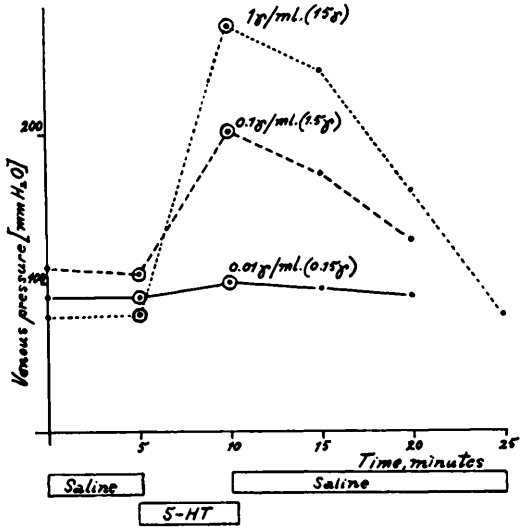

FIG. 1. Relation of concentration to local veno-pressor effect of 5-hydroxytryptamine creatinine sulfate (5-HT). (See text.)*

* Total volume of 15 ml was inj. each 5 min. period at constant speed of 3 ml/min. Increasing concentrations of 5-HT induced more pronounced and sustained pressor effects. The curves traced were drawn from avg of 6 experiments.

(3), have followed further intermittent administration of 5-HT. Two individuals received 330 γ of 5-HT per minute in a volume of 1.66 ml/min. over a period of 30 minutes

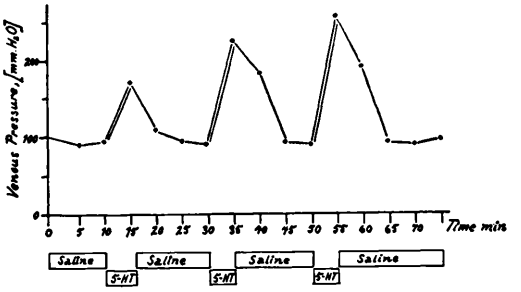

FIG. 2. Local veno-pressor effect of repeated administration of 5-hydroxytryptamine creatinine sulfate. (See text.)

for a total dose of 10,000 γ. Speed of infusion was then doubled, the same total dose of 5-HT being injected within 15 minutes (Fig. 3). A maximum effect was quickly reached; further administration of the drug maintained, but did not significantly enhance, the veno-pressor effect. There was no elevation of systemic venous or arterial pressure.

(c) *Effect of rapid intravenous and intra-arterial administration of high doses of 5-HT.* Two typical studies are reported. A healthy, 16-year-old girl received *intravenously* 1,000 γ of 5-HT in 5 ml of saline in one minute time. Within 15 seconds, she experienced pain at site of injection, flushing sensation limited to face and neck for 2 to 3 minutes. Arterial

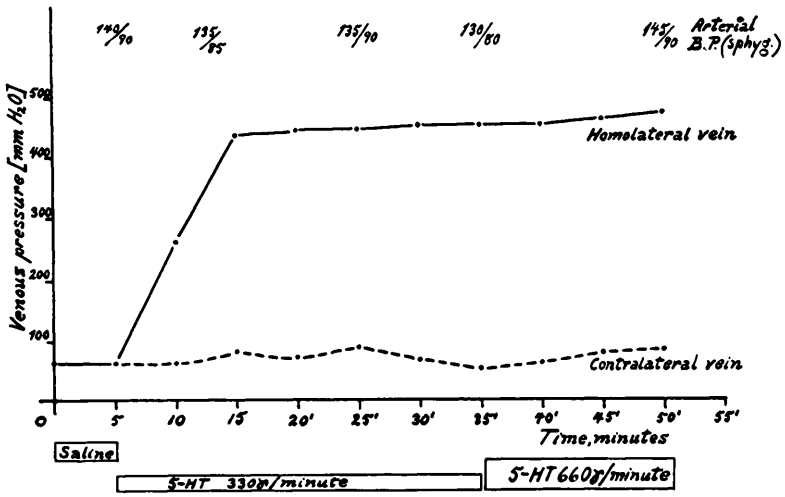

FIG. 3. Effect of continued administration of high doses of 5-hydroxytryptamine creatinine sulfate (5-HT) on pressure in homolateral and contralateral vein, and on arterial pressure (sphygmomanometric reading, values in mm Hg).* Graphic representation of an experiment G.M., a patient of Hodgkin's sarcoma in remission.

* A total of 10 mg of 5-HT was administered intravenously in 30 min.; then same amount was given in 15 min. by doubling speed of administration.

blood pressure rose from 130/64 to 150/110 mm Hg within 1 minute of the injection and returned to normal within 2 minutes. No rise of systemic venous pressure was noted. A 50-year-old male with generalized carcinomatosis received the same amount of 5-HT, *intraarterially*. Severe but fleeting pain followed immediately, radial pulse could not be felt for 5 minutes. After a short period of blanching, skin of volar and dorsal surface of the hand appeared flushed for longer than 30 minutes. Pressure rose from 117/80 to 130/86 mm Hg at the end of the injection; dropped to 100/60 mm Hg at the end of 5 minutes, returned to normal within 10 minutes. Pressure in the *homolateral vein* rose from 65 to 280 mm H_2O. Readings after 5′ 10′, 20′ and 25′ were 190, 155, 120 and 75 mm H_2O respectively. Again *there was no rise of pressure in the contralateral vein.*

(d) *Vasopressor effect of intravenous 5-HT in one patient with venous-arterial shunt.* A patient with ventricular septal defect and cyanosis was studied.‖ One ml of solution containing 200 γ of 5-HT was injected in one antecubital vein in one minute, a dose not followed by significant systemic effect in normal individuals. In this patient, however, injection induced immediate generalized "flushing" sensation and numbness. Arterial pressure rose from 110/80 to 125/100 mm Hg for about 5 minutes following the injection. Venous pressure recorded in the opposite arm remained unchanged.

Discussion. The drug 5-HT stimulates contraction of smooth muscle fibers(4), an attribute which may explain the local venopressor effect observed in our experiments. Vasopressor effect was obviously related to the concentration of 5-HT in each segment of the circulation at any given time. High doses given i.v. in very short time caused maximum local venopressor response and significant but only fleeting response in arterial pressure; administered over a longer period of time they induced only local venopressor effect. Fig. 1 and 2 indicate that the effect was specific rather than due to such non-specific phenomena as reflex venoconstriction due to pain or filling of the vein by solutions. Striking was the inability of 5-HT given intravenously at standard doses to affect systemic arterial pressure, the only exception being represented by the patient with venous-arterial shunt. Also, even large amounts of 5-HT given intravenously did not induce elevation of systemic venous pressure. Finally, intraarterial administration of 5-HT caused a sustained response in the homolateral, but not in the contralateral vein.

A number of speculative conclusions suggest themselves. Because of its fleeting action, 5-HT must be disposed of by the body quickly. *In vitro* experiments suggest that 5-HT may not be destroyed by aminoxidase (2). Partial by-passing of the pulmonary circulation (venous-arterial shunt) caused elevation of arterial blood pressure and generalized flushing at doses unable to do so in normal subjects. 5-HT may thus be retained within the lungs. Also, since the intraarterial injection of 5-HT was followed by sustained elevation of pressure in the homolateral vein, 5-HT might have been retained in and slowly released from the peripheral capillary bed. Storage in the pulmonary and peripheral capillary districts may then represent an important factor in the inactivation of injected 5-HT.

It has been shown that platelets absorb and carry 5-HT within the circulation(5). If platelets are trapped in the pulmonary as well as in the peripheral circulation, they may then retain and later slowly release absorbed 5-HT. Tissues also may possess a similar property.

Summary. 1. Intravenous injection of 0.3 γ/min. 5-hydroxytryptamine creatinine sulfate (5-HT) caused transitory elevation of local venous pressure; higher doses induced more marked elevation of local venous pressure and, when administered in short period of time, of arterial pressure. Elevation of systemic venous pressure was not obtained even with extremely high doses of 5-HT. 2. Intraarterial administration of 5-HT induced sustained elevation of pressure in the homolateral veins (30 minutes or longer). 3. Elevation of arterial pressure and generalized

‖ This patient became available for study through courtesy of Dr. Richard H. Wright.

flushing followed injection into a patient with septal venous-arterial shunt of a dose of 5-HT unable to cause such effect in normal subjects. 4. It is postulated that injected 5-HT is quickly removed from the circulation, perhaps by platelets or by other cellular elements retained in capillary beds and released slowly at a later time.

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Leukemia Induction in Mice by Fast Neutron Irradiation.* (22501)

A. C. UPTON, G. S. MELVILLE, JR., M. SLATER, F. P. CONTE, AND J. FURTH.†

Biology Division, Oak Ridge National Laboratory, Oak Ridge, Tenn.

This investigation was undertaken for the purpose of studying development of lymphoid, myeloid, and other types of leukemia in mice exposed to fast neutrons, as compared to X rays. Most cases of radiation-induced leukemia in human beings have resulted from exposure to gamma or X rays(1); however, in Japanese atomic bomb survivors the possible importance of neutron irradiation in the production of leukemia has been cited(2). Because neutrons have been observed to be, in general, relatively more effective than X or gamma rays in causing delayed radiation injuries in mice(3,4) and in man(5), determination of the relative biological effectiveness (RBE) of neutrons for leukemia induction is of practical, as well as fundamental importance.

Materials and methods. Male and female mice of the RF strain 8-16 weeks of age were exposed to fast neutrons in the 86-inch cyclotron of the Oak Ridge National Laboratory or to X rays. The neutrons, produced by the bombardment of an internal beryllium target with 22-Mev protons, had an average effective energy of approximately 1 Mev. The factors of X radiation were as follows: 250 kvp, 30 ma, TSD 93.7 cm, filtration 3 mm of Al (plus beryllium window), hvl 0.4 mm of Cu. Neutrons and X rays were administered to the whole body at an intensity of 65-115 rad min in a single exposure or in two equal treatments separated by an interval of 2-8 days. Further details of the dosimetry and methods of exposure have been reported(6,7). After irradiation the mice were caged in groups of 8-10 in air-conditioned quarters, with Purina fox chow and drinking water available *ad libitum*. The animals were observed until natural death or were sacrificed *in extremis*. Postmortem examinations were performed on all mice.

Results. For a given dose of radiation the 30-day mortality was greater in neutron-exposed than in X-irradiated mice; in females the $LD_{50}/30$ days for a single exposure was approximately 335 rad of neutrons or 490 rad of X rays (RBE = 490/335 = 1.47)(7). With fractionation of the dose into two equal exposures, the $LD_{50}/30$ days for X rays and neutrons increased with the interval between treatments, being approximately 640, 710, 815, and 870 rad of X rays for intervals of 2, 4, 5, and 8 days, respectively(8). The acute injuries produced by neutron irradiation were indistinguishable from those caused by X rays except for acceleration of the 30-day mortality (the peak death rate occurred on the 5th day after single median-lethal neutron irradi-

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† Present address: Children's Cancer Research Foundation, Boston, Mass.