Quantitation of Monoamine Oxidase Inhibition Produced with Various Drugs in Man.* (25567)

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Use of monoamine oxidase (MAO) inhibitors in treatment of such clinical conditions as psychic depression(1), hypertension(2,3), angina pectoris(4,5) and rheumatoid arthritis (6) constitutes a new and promising area of therapeutics. It seemed important to determine the enzyme-inhibiting potency of these newly-developed agents in man as well as to clarify the relationship between MAO inhibition and alleged therapeutic effects. To aid in accomplishing this, 2 methods were devised to quantify MAO inhibition in the human. The first consisted of measuring percentage of oral dose of serotonin excreted as urinary 5-hydroxyindoleacetic acid (5HIAA), before and after administration of a presumed MAO inhibitor(7). Secondly, we found that measurement of urinary excretion of tryptamine affords a convenient and sensitive method of estimating MAO inhibition in man(8). This report presents the effects of several MAO inhibitors of current clinical interest on excretion of tryptamine.

Methods. The subjects were 15 patients with uncomplicated hypertension. Twenty-four hour collections of urine were obtained during control and experimental periods and tryptamine was measured by method already reported(8). Five compounds designated as MAO inhibitors from animal studies were evaluated; these were iproniazid (Marsilid), B-phenylisopropylhydrazine (JB-516, Catron), *DL - phenylcyclopropylamine* (SKF-385), N-(2-(Benzylcarbamyl) ethylamino)-isonicotinamide (nialamide, Niamid) and phenelzine (Nardil). Dosage schedules included those suggested by the manufacturers and except for iproniazid the recommended daily dosage was exceeded to 2-fold in each instance to observe "maximal" enzymatic effects. The drugs were administered orally in single daily doses (iproniazid, JB-516) at beginning of each day's urine collection (8 a.m.) or initially in single daily doses and subsequently at 12, 8 or 6 hour intervals (SKF-385, nialamide and phenelzine). A specific dosage was maintained 5 to 14 days and changed only after daily excretion of tryptamine appeared constant. The tryptamine values for each dose-schedule were then recorded as the range occurring at time a new plateau had been reached.

Results. For purposes of comparison, alterations in urinary tryptamine and excretion of 5HIAA following oral administration of serotonin in a patient receiving JB-516 are shown in Fig. 1. A 70% inhibition of serotonin conversion to 5HIAA corresponded to a 5-fold increase in urinary tryptamine in this case.

Fig. 2 represents tryptamine excretion in another patient before and during administration of JB-516 and nialamide, the drugs given at separate periods of time. Daily excretion of tryptamine during administration of 25 mg/day JB-516 reached levels of 500-600 μg/day while a daily dose of 200 mg nialamide was required to produce a similar effect. Increasing the dosage of JB-516 to 50 mg/day failed to result in a proportionate increase of urinary tryptamine.

Table I is a summary of alterations in urinary tryptamine produced by various doses of the 5 inhibitors studied. A satisfactory dose-response relationship is apparent from the mean values of each group, particularly in the case of nialamide and SKF-385. However, it is also apparent that a rather wide range of values was obtained in different cases with a given dose of an inhibitor. A more reliable index of MAO inhibition for a given dose of drug results from expressing the ratio of average level of tryptamine excretion during experimental period to average level during con-

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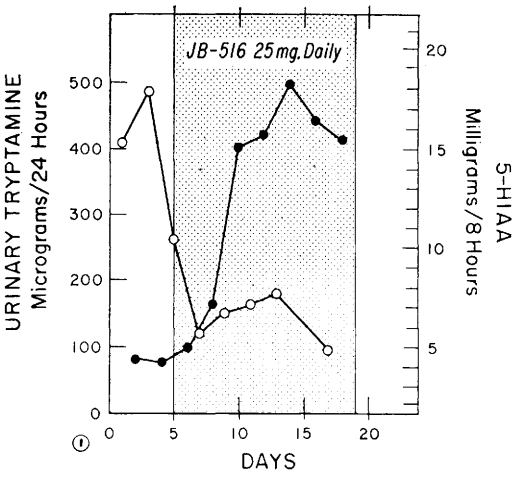

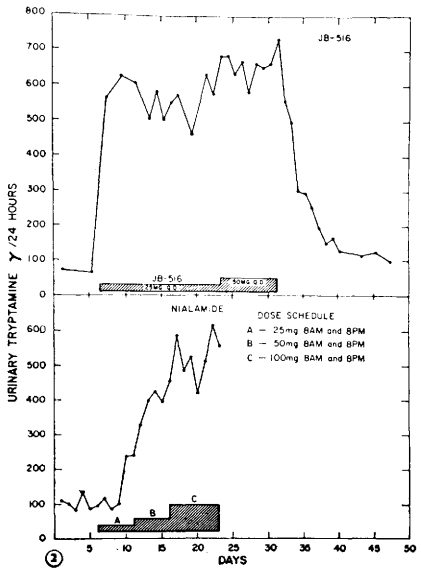

FIG. 1. Comparison of rise in tryptamine excretion (●) to fall in 5-HIAA excretion (○) during JB-516 administration.

FIG. 2. Urinary tryptamine excretion during sequential administration of JB-516 and nialamide in same patient.

trol period in each case individually. This obviates the variability of control levels of tryptamine excretion from patient to patient. An average of individual ratios at a given dose results in a mean ratio for the entire group. Range of individual ratios and mean ratios for each dose group is listed in last column in Table I.

A detailed account of other effects observed is beyond the scope of this paper. No overt psychic alterations were detected. A postural lowering of blood pressure was observed with 60-80 mg/day SKF-385, 120 mg/day phenelzine and in all cases to which JB-516 was administered. No alteration of blood pressure occurred with the reduced dose of iproniazid used or with nialamide at doses employed.

Discussion. These studies establish the drugs included in this report as MAO inhibitors in man. The daily doses of these agents, purported to give favorable results in psychiatric patients, are also the doses which result in at least a 4-fold increase in daily excretion of tryptamine (*e.g.* JB-516 - 12.5 mg; nialamide - 100-150 mg, and phenelzine - 60 mg). With the exception of nialamide, similar doses of the various drugs appear to produce a postural lowering of blood pressure in human hypertensives. It is important to note that nialamide, at doses used, failed to alter blood pressure even though tryptamine excretion was similar in amount to that observed with doses of other inhibitors which cause lowering of blood pressure. We have recently found, however, that higher doses of nialamide (400-500 mg/day) result in orthostatic lowering of blood pressure in hypertensives.

While increases in urinary tryptamine may not be exactly proportional to the effects of MAO inhibitors in every tissue, the method is simple and is nearest to a chemical test reflecting therapeutic activity now available. Also, conclusions can be drawn from studies on relatively few patients. The test appears to be quite sensitive, although it is not known to what extent MAO is actually inhibited in tissues at various levels of tryptamine excretion. It will be interesting to determine this on biopsy and autopsy material.

Other factors affecting use of urinary tryptamine as index of MAO inhibition have been discussed(8). One of these is the possibility of inhibition of tryptophan decarboxylation to tryptamine as might be expected to occur with certain hydrazine compounds; urinary tryptamine levels would thus fail to rise as much as with MAO inhibition alone. Also excretion of drug metabolites may interfere with the fluorimetric assay of tryptamine. In these respects the serotonin test may still be useful because of its specificity in indicating MAO

TABLE I. Effect of Various Doses of MAO Inhibitors on Urinary Tryptamine.

Drug	Daily dose (mg)	No. cases (No. determ.)	Urinary tryptamine (μg 24 hr) Range	Mean	Urinary tryptamine ratio,* avg during therapy/control avg Range (individual)	Mean (group)
Control		15 (59)	30– 111	63 ± 22†		
JB-516	12.5	2 (7)	115– 618	313	2.7– 7.0	5.3
	25	9 (54)	245– 750	484	5.2–10.0	7.2
	50	1 (9)	656– 825	704	11.3–14.2	12.1
Nialamide	50– 60	4 (15)	100– 234	157	1.7– 4.0	2.4
	100–120	5 (31)	209– 540	315	2.3– 7.8	4.3
	150	2 (8)	353– 515	444	6.2– 7.2	6.5
	200	4 (27)	337– 975	558	5.9–12.3	7.9
SKF-385	10	3 (9)	87– 159	120	1.5– 1.8	1.6
	20– 30	4 (14)	189– 544	281	2.2– 6.9	3.8
	40	2 (13)	255– 517	402	3.5–10.6	6.2
	60– 80	2 (21)	466–1030	719	5.6–13.0	10.6
Phenelzine	45	1 (5)	69– 100	85	1.3– 2.0	1.6
	60	2 (8)	120– 251	184	2.3– 6.1	4.0
	120	1 (3)	177– 512	299	4.3–12.5	7.3
Iproniazid	50	2 (15)	91– 231	161	1.0– 2.6	2.2

* See text for explanation. † One stand. dev.

inhibition and the fact that few agents interfere with assay of 5HIAA. Additionally, one may measure the increase in excretion of another amine, tyramine(9), where metabolism is also primarily dependent on MAO.

Summary. An increased urinary excretion of tryptamine occurred in human hypertensives during treatment with 5 monoamine oxidase inhibitors. Doses of drugs purported to produce comparable clinical effects, appear to have approximately equivalent enzymatic effects as indicated by changes in urinary tryptamine. It is recommended that biochemical observations of this type be included in further studies on therapeutic effects of these agents.

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