Effect of Phenylbutazone (3,5-dioxo-1, 2-diphenyl-4-n-butyl-pyrazolidin) on Renal Function. (20685)

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Phenylbutazone, a potent analgesic, anti-inflammatory agent, has had extensive use in patients with painful disorders of joints. Up to 20% of patients receiving this drug have been noted to develop edema, the actual number apparently depending upon the vigor of scrutiny. It has been demonstrated that retention of salt and water with accompanying weight gain is an almost constant, immediate, and sustained effect which is not mediated through reduction in glomerular filtration rate (1,2). Only 2 of 18 patients carefully followed at this hospital failed to gain weight. That the effect is immediate can be demonstrated by a sharp reduction in urine output and an average weight gain of 2 lb during the first 24 hours of therapy. This continues daily for 5 or 6 days until the patient has gained an average of 10 to 16 lb. It is sustained until the drug is stopped, at which time a spontaneous diuresis with weight loss occurs. The present study was undertaken in an attempt to clarify further the mechanism of this salt and water retention.

Materials and methods. The renal clearance of inulin (C_{IN}) and para-aminohippurate (C_{PAH}) was determined in 8 patients before and after institution of Phenylbutazone therapy. In 4 of these, maximum tubular excretion of para-aminohippurate (Tm_{PAH}) was also done. The patients were males 18 to 46 years of age who were admitted to the hospital for treatment of arthritis. Four of these patients had rheumatoid spondylitis; 3 had early minimal to moderate rheumatoid arthritis; and 1 patient had gout. Phenylbutazone therapy consisted of 800 mg daily, orally, in 4 equal doses in all except 1 patient who received 1 g daily, intramuscularly. The clearances were done in the morning postabsorptive state following liberal water ingestion to insure adequate urine flow. The clearance technics employed were those used by Goldring and Chasis (3). Clearances were performed on the 3rd or 4th day of Phenylbutazone therapy since the peak of salt and water retention effect seemed to occur at this time. Six additional patients free of renal disease and receiving para-aminosalicylic acid in doses of 12 g daily, orally, for pulmonary tuberculosis were selected for study. Oral therapy was replaced by 10 g of PASA intravenously, given over a period of 30 minutes at a recorded time each morning for 5 mornings. The intravenous route was chosen to assure complete absorption and to avoid the complications of nausea and vomiting which sometimes occur during oral therapy. At exactly 4 and 7 hours after the initiation of intravenous infusion, samples for the determination of PASA blood levels were drawn. Phenylbutazone, 1 g daily, intramuscularly, was given on the evenings pre-

TABLE I. Renal Clearances before and during Phenylbutazone Therapy.

	Inulin clearance, cc/min.*		PAH clearance, cc/min.*		TmPAH, mg/min.*	
	Before	During	Before	During	Before	During
T.	113†	117	595	347		
	100†	105	—	339		
S.	147	145	782	501		
	179	115	1354	427		
T.	123	117	945	321		
	104	91	782	299		
G.	132	88	591	533		
	128	86	601	489		
	100	—	510	—		
L.	143	102	907	496	—	
	131	93	838	567	—	
	150	103	—	—	133	32
D.	132	145	916	465	—	
	124	122	961	449	—	
	127	132	—	—	110	24
F.	130	143	959	724	—	—
	153	125	1108	605	—	—
	126	140	—	—	137	68
S.	151	144	996	558	—	—
	141	147	878	627	—	—
	133	133	—	—	131	26

* Not corrected for body surface area.

† Consecutive vertical figures for each patient represent consecutive 15 min. urine collection periods.

ceding the 3rd, 4th, and 5th day of this regimen. PASA blood levels were determined by the Method of Marshall(4).

Results. Table I summarizes the results of the renal clearances of inulin (C_{IN}) paraaminohippurate (C_{PAH}), and the maximum tubular excretion of PAH (Tm_{PAH}) in the 8 patients studied. There is no significant change in the glomerular filtration rate. However, it will be noted that there is a constant reduction of C_{PAH} in all except 1 patient (G). This patient is the only one of the group who had gouty arthritis. In the 4 patients in whom Tm_{PAH} was determined before and during Phenylbutazone administration, a marked and constant decrease of 50% or more is noted. All of these patients gained from 10 to 16 lb of weight during the first week of Phenylbutazone therapy. Only 2 developed actual edema. In S., this was manifested as morning puffiness of the face and periorbital swelling. F. T. developed swelling of the ankles toward the end of the day.

Chart I plots the fall in PASA blood levels from the fourth to seventh hours following intravenous injection of this drug. Table II tabulates a 2-day average for PASA blood levels before institution of Phenylbutazone and a three-day average during Phenylbutazone administration in 6 patients. No real difference in the levels before and during Phenylbutazone is apparent. Due to the intravenous route of administration, levels are high and the fall rapid. The small differences noted are within the range of error of the method used.

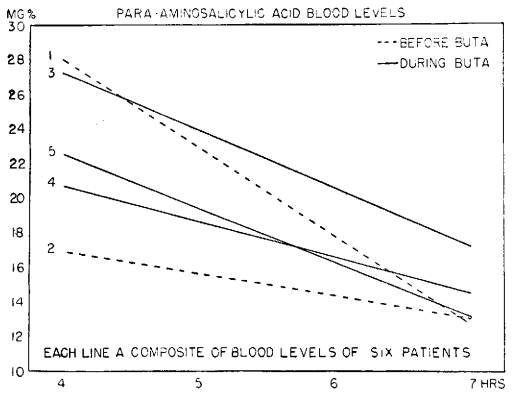

CHART I. Effect of phenylbutazone on "para-aminosalicylic acid blood levels." Numbers 1 through 5 refer to consecutive days of study. Phenylbutazone started on 3rd day.

TABLE II. Para-aminosalicylic Acid Blood Levels before and during Phenylbutazone Rx.

Patient	Hour*	Before,† mg %	During,‡ mg %
R.	4th	24.1	25.1
	7th	15.4	16.0
G.	4th	25.8	24.8
	7th	15.5	18.2
C.	4th	16.5	15.5
	7th	12.1	12.1
S.	4th	23.5	23.6
	7th	14.7	15.9
G.	4th	18.1	19.4
	7th	12.6	13.1
M.	4th	23.8	25.8
	7th	12.2	15.8

* Hours following PASA intravenously administered.
† Each figure a composite of 2 days blood levels.
‡ " " " " " 3 " " " .

Discussion. The reduction of C_{PAH} by Phenylbutazone in the first 4 patients suggested that a reduction had been effected in renal plasma flow. However, a specific inhibition of tubular excretory activity was quite possible and could not be excluded, except by extraction studies or quantitative excretory studies.

It is believed that the marked reduction noted in Tm_{PAH} during Phenylbutazone administration confirms an inhibition of tubular excretory activity. The knowledge that another tubular depressant (Benemid) decreased the secretions of both para-aminohippurate and para-aminosalicylic acid(5) led us to study the effect of Phenylbutazone on PASA excretion also. It is surprising that there was no apparent inhibition of PASA excretion. It must be admitted that a 2-point curve of 4 and 7 hours is not complete, yet Benemid effects are conclusive when so plotted. One might speculate that the effect of Phenylbutazone on PAH excretion is not that of inhibition of a selective tubular transport mechanism.

There is mounting evidence that the effect of Phenylbutazone is a more general one of depression of cellular metabolism. Kuzell reported that this drug inhibited oxygen consumption of rat cerebral tissue slices in direct proportion to its concentration(6). Werner reports a personal communication from Engle-

man that this drug inhibits transiently the accumulation of I^{131}(7). Certainly, cellular respiratory studies are in order, and renal oxygen uptake determinations before and during Phenylbutazone administration would be helpful.

Excretory studies of other renal tubular substances would be enlightening, especially of sodium. From clinical studies, it might be assumed that tubular reabsorption of sodium is increased. If so, this is indeed paradoxical since mercurial diuretics inhibit tubular excretion of PAH and decrease reabsorption of sodium.

Conclusions. 1) Phenylbutazone causes retention of salt and water in approximately 80% of patients receiving this drug with clinical edema becoming manifest in approximately 10%. 2) Phenylbutazone markedly depresses renal tubular excretion of para-aminohippurate. 3) Excretion of para-aminosalicylic acid does not appear to be inhibited by this drug. 4) Further studies are needed to clarify the relation, if any, between decreased excretion of para-aminohippurate and the clinically observed increased reabsorption of sodium.

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Effect of Ethionine and Other Materials on Semliki Forest Virus Infection in the Mouse.* (20686)

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Semliki forest virus was isolated by Smithburn and Haddow(1) from mosquitoes collected in Uganda. Although the virus has not been recovered from man, antibodies for it have been demonstrated in human serum specimens collected in Uganda and in India (2,3). In mice, the virus produces a fatal disease following inoculation by the intracerebral, subcutaneous, intramuscular or intraperitoneal routes(1). Animals inoculated intracerebrally with the virus usually die within one week and within 2 weeks after intraperitoneal inoculation. Paralysis of one or both posterior extremities usually constitutes the first sign of infection but hyperirritability and convulsions may occur. Animals may recover from paralysis.

Since the peripheral inoculation of mice with Semliki forest virus produces a disease involving the central nervous system, this virus provides a useful means for the investigation of materials which may alter resistance of the mouse to neurotropic viruses. The Semliki forest-mouse model has been used in a study involving a number of amino acids, purines, pyrimidines, and thiosemicarbazones. The most significant results were obtained with DL-ethionine and 5-phenoxythiouracils.

Materials and methods. The strain of Semliki forest virus used in these experiments was obtained in 1951 from Dr. H. M. Powell of Lilly Research Laboratories who, in turn, had received it from Dr. Smithburn. Five intracerebral passages in mice have been

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