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Effect of Carbonic Anhydrase Inhibitor (6063) on Arterial-Alveolar CO_2 Gradient in Man.* (20587)

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Inhibitors of carbonic anhydrase activity have been employed in the effort to block the *in vivo* reaction, $H_2O + CO_2 \rightleftharpoons H_2CO_3$. Various physiological mechanisms are dependent upon this reaction. Höber(1) first demonstrated that sulfonilamide, a carbonic anhydrase inhibitor, impairs the acidification mechanisms of the frog kidney. The use in the dog of stronger sulfonamide inhibitors, especially Diamox (6063 or 2-acetylamino-1, 3,4-thiadiazole-5-sulfonamide), has implicated carbonic anhydrase in the secretion of hydrochloric acid by the stomach(2) and of bicarbonate by the pancreas(3). It has been recently shown(4) that Diamox increases plasma bicarbonate concentration and pCO_2 in marine fishes, an effect possibly attributable to inhibition of erythrocyte carbonic anhydrase.

Roughton(5) showed that carbon dioxide exchange in unanesthetized humans was impeded when sulfonilamide was combined with exhaustive exercise. In anesthetized dogs(6), Diamox is reported to interfere with CO_2 transport, possibly by inhibition of the erythrocyte enzyme system. It was the purpose of this study to determine whether the carbonic anhydrase inhibitor, Diamox, in concentrations adequate to inhibit renal acid excretion, would interfere with the transport of CO_2 from pulmonary capillary blood into the alveoli in normal, non-anesthetized human subjects.

The subjects were 3 convalescent patients without cardiac, renal, or pulmonary diseases from the First (Columbia University) Medical Division of Bellevue Hospital. These pa-

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TABLE I. Effects of Diamox (6063) on Resting Man.

	Time, min.	Urine V, ml/min.	Urine Bicarbonate, mM/L	Urine $U_{Na}V$, μEq/min.	Urine U_KV, μEq/min.	pH	C_{CR}	Respiratory gases V_E, M^2/BSA	Respiratory gases $P_A CO_2$, mm Hg	Respiratory gases RQ	Arterial blood pH	Arterial blood $Pa CO_2$, mm Hg	Arterial blood Total CO_2, mM/L
Subject A:	0	.9		229	89	7.41	128	4.12	43	.89	7.39	46	24.2
Control	10	.7	39.1			7.35*		3.98	41	.87	7.39	45	24.2
Subject A:	30												
After Diamox	72	5.3		638	244	7.75	137						
	83	13.7		700	288	7.66							
	86	15.3	33	596	231	7.30*	130						
	100	14.0		567	213	7.47							
	117	8.3		590	222	7.64	130						
	125	5.6	57	586	180	7.51*	134	4.02	40	.81	7.37	42	21.5
	160	2.9				7.74	134	4.01	38	.76	7.35	40	20.5
Subject B:	0							3.67	39	.83	7.40	40	23.8
Control	12							3.77	40	.81	7.41	41	23.2
Subject B:	120							3.55	40	.81	7.38	37	22.2
After Diamox	150							3.62	38	.80	7.37	39	22.0

* Collected under oil.

TABLE II. Effects of Diamox (6063) on Man during Mild Exercise.

	Time, min.	Urine V, ml/min.	Urine Bicarbonate, mM/L	Urine $U_{Na}V$, μEq/min.	Urine U_KV, μEq/min.	pH	C_{CR}	Respiratory gases V_E, M^2/BSA	Respiratory gases V_{O_2}, M^2/BSA	Respiratory gases RQ	Arterial blood pH	Arterial blood $Pa CO_2$, mm Hg	Arterial blood Total CO_2, mM/L
Rest	0	.7		50		6.81	133	4.98	141	.89	7.41	42	23.4
Exercise	45	3.3	4.35	51	41.4	6.73	140	6.9	267	.82	7.41	42	23.0
Diamox	54												
Rest	75	5.77		165	180	7.3	156	4.33	146	.80	7.39	42	20.3
	110	7.22		446	380	7.7	148						
	125	4.34	54.8	335	293	7.7	126						
Exercise	147	3.64	55.2	396	298	7.8	138	6.68	253	.81	7.36	44	21.8
	212	2.19		314	234	8.0	123						

tients were trained by repeated cardio-pulmonary studies until they could relax with constant oxygen consumption and RQ despite arterial puncture and gas collection. Two of the subjects were studied at rest, the other was also studied during a steady state of mild, active leg exercise.

Methods. After a period of rest an indwelling urethral catheter and brachial arterial needle were placed in position. Observations were begun ½ hour later. Expiratory gas, arterial blood and urine were collected and analyzed according to methods described elsewhere(7). End expiratory gas was collected by a Rahn(8) sampler and analyzed for CO_2 and O_2 using the micro-Sholander gas apparatus. Blood and urine CO_2-contents were determined by the method of Van Slyke and Neill(9). Arterial blood pCO_2 was calculated from the CO_2 content, pH and per cent oxygen saturation, using the line charts of Van Slyke and Sendroy(10), pH was determined directly by the McInnes-Belchen glass electrode. Potassium and sodium concentrations were determined by an internal standard flame photometer. Glomerular filtration rate was estimated from the endogenous creatinine clearance (C_{CR}) using the method of Bonsnes and Taussky(11). After 2 control periods, 50 mg per kg body weight of Diamox‡ were administered orally. This dose is approximately 5 times that needed to produce an alkaline urine in man, as reported by others. Observations were then repeated one and 2 hours later.

Results. In the resting subjects, Diamox caused an increase in the excretion of sodium, potassium and bicarbonate, and an increase in urine flow. (Table I). These renal effects were not associated with any change in minute ventilation V_E, oxygen consumption V_{O_2}, respiratory exchange ratio (RQ), arterial or alveolar carbon dioxide tension (Pa_{CO_2} and PA_{CO_2}). Mild exercise, sufficient to double the oxygen consumption, did not reveal any impairment in the elimination of carbon dioxide (Table II).

These observations demonstrate that in the resting subject, Diamox may have a substantial renal effect with no interference with the passage of CO_2 from pulmonary capillary blood into alveoli. The combination of Diamox plus increased CO_2 production induced by mild exercise also failed to impede CO_2 elimination into the alveoli. This failure to influence pulmonary CO_2 excretion may be due to the large concentration of carbonic anhydrase in the human erythrocyte as compared to other tissues.

Summary. Diamox (6063) was administered per os to 3 human subjects without pulmonary disease in single doses of 50 mg per kg body weight. This dose elicited typical renal effects (diuresis and increased excretion of bicarbonate, sodium and potassium) but failed, even when combined with mild exercise, to interfere with CO_2 elimination from pulmonary capillary blood into alveolar air.

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