Failure to Confirm a Prolongation of the Biological Half-life of \(^{22}\text{Na}\) in Hypertensive Patients

By Lewis K. Dahl, M.D., Louis C. Lax, M.D., Charles R. Young, M.D., Eckart Schackow, M.D., and Knud D. Knudsen, M.D.

ABSTRACT

The biological half-life of \(^{22}\text{Na}\) was measured in 29 patients with uncomplicated essential hypertension and 15 patients with normal blood pressure. All were on a standard regimen with constant diet and known NaCl intake. The biological half-life of \(^{22}\text{Na}\) was found to be similar in those with and without hypertension. This larger series of observations failed to confirm an earlier study from our laboratory in which the biological half-life of \(^{22}\text{Na}\) was reported to be longer in individuals with hypertension. The most likely explanation for the difference is that with the small number of patients studied earlier, there was a fortuitous selection of normotensive subjects with a shorter biological half-life for \(^{22}\text{Na}\).

ADDITIONAL KEY WORDS

normotensive subjects essential hypertension

A small series of patients with essential hypertension was reported earlier as having a longer biological half-life of \(^{22}\text{Na}\) than normotensive subjects (1, 2). Lean-body mass, estimated from total body K, was related to total exchangeable sodium and this calculation suggested that the hypertensive patients might have an enlarged pool of exchangeable sodium. Since biological half-life is a function of intake and available sodium in the body, these calculations were in keeping with the prolongation of the half-life of \(^{22}\text{Na}\). However, the earliest publications of Dole et al. (3), those of our own (4), and those of most (5-8) but not all (9) other investigators indicated that the sodium pools of hypertensive patients were not increased.

This disparity led to the present study, in which a much larger number of both hypertensive and normotensive subjects was investigated. The disparity was reconciled by showing that the biological half-life of \(^{22}\text{Na}\) was not regularly increased in hypertensive patients.

Materials and Methods

**GENERAL**

Two separate studies were made on different sets of patients but the results have been combined in this paper. In Study 1 the biological half-life was determined while the patients received each day 5 g of enteric-coated tablets of NaCl, in addition to a basic diet containing approximately 300 mg NaCl. Measurements of total exchangeable Na and K were also made, to control the earlier indirect calculations (1, 2) that the longer biological half-life was due to a larger "metabolic pool" of Na. These data have not been included here because the premise on which the study was based (a regularly prolonged biological half-life for \(^{22}\text{Na}\) in hypertensive subjects) was not confirmed, and because all values for total exchangeable Na and K were within the normal ranges reported earlier (3-8). Furthermore, there was no statistically significant difference between hypertensive and normotensive subjects in the values for total exchangeable Na and K, or the ratio of the two.

Study 2 was undertaken when the results of Study 1 failed to confirm the original observations (1, 2). Reexamination of the data from the original study suggested that the difference in biological half-life might be brought out by a higher intake (10 g/day) of NaCl. In addition,
in order to avoid the possibility of irregular absorption of the enteric-coated tablets of NaCl, the patients drank 1175 ml of normal saline solution containing 10 g NaCl (171 mEq Na) each day. The total daily NaCl intake from diet plus saline was therefore 10.3 g. Except where indicated, the two studies were otherwise the same.

PATIENTS

Hypertensive Patients

The severity of the hypertension varied considerably, but all patients were ambulatory; none had malignant hypertension or renal or cardiac failure as judged by history or examination. All of the subjects were thought to have "essential" hypertension because known causes of high blood pressure were excluded in every case by appropriate clinical tests: Renal arteriography or 181I Hippuran® renograms (sodium o-iodohippurate) or both were used when necessary to help exclude renal arterial or parenchymal disease. Every subject had negative results for the phentolamine or histamine test for pheochromocytoma as well as a normal 24-hour excretion of catecholamines. Except for variable and mild albuminuria in some, the renal function in all was within normal limits as indicated by results of routine urinalysis, intravenous urography, urea clearance, and blood concentrations of urea nitrogen and creatinine. None of the subjects received antihypertensive medication during the time of the study.

In Study 1, data from 18 patients (9 women, 9 men) were included in the calculations; 3 others were studied but excluded because their blood pressures became "normal" (i.e., consistently less than 140 mm Hg systolic or 90 mm Hg diastolic) during the study. Pertinent data are shown in Table 1. In Study 2, data from 11 hypertensive patients (6 women, 5 men) were included (Table 2). Five were studied but were excluded, 4 because they became "nonnotensive" during the study, and a 5th had chronic renal disease.

Normotensive Subjects

There were 5 control subjects (3 women, 2 men) in Study 1, and 10 in Study 2 (9 women, 1 man). Pertinent data are included in Table 1. In both studies, the normotensive subjects were volunteers who were not taking antihypertensive medication at the time of study.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (yr)</th>
<th>Sex</th>
<th>Weight (kg)</th>
<th>Mean B.P. (mm Hg)</th>
<th>Biological half-life, (days)</th>
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23.2 ± 3.3 SEM*

II. 5 Normotensive subjects

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<th>Weight (kg)</th>
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<th>Biological half-life, (days)</th>
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21.0 ± 4.5 SEM*

*t = 1.18; P > 0.2.
Clinical Data and Biological Half-Life in Patients with and without Hypertension Taking 10.3 g NaCl Each Day (Study 2)

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$^{*} t = 1.84; 0.10 > P > 0.05.$

1 man). The 3 subjects in Study 1 with hemiplegia following cerebrovascular accidents were known to have had normal blood pressures prior to the cerebrovascular accident. Except for tests for pheochromocytoma, the control patients had the same examination and tests as those with hypertension. None was taking drugs that would have modified electrolyte excretion. All were ambulatory, although E. E. (Table 1) required supervision when he walked because he had severe hemiplegia.

**REGIMEN AND DIETS**

With minor modifications these were the same as in our previous study (1,2). Briefly, each subject was on a constant, low sodium diet (5 to 7 mEq/day, equivalent to approximately 300 to 400 mg NaCl) beginning 1 to 2 weeks prior to administration of the isotope and extending through the 2- to 4-week period in which data were collected. Diets, while very similar, were not identical among all subjects but were constant for each individual. Caloric intake was fixed at a level to maintain weight. In Study 1, 24-hour excretion of sodium in the urine was checked frequently but not daily; in Study 2, urine was collected for each 24-hour period and measured for sodium. No evidence of deviation from the program or of side effects from the saline was found.

Blood pressures (subjects recumbent) were measured six mornings a week under standard conditions with a mercury sphygmomanometer. Systolic and diastolic pressures were recorded as the first and fourth phases, respectively. "Mean blood pressure" was calculated as half the sum of systolic and diastolic pressures. The mean blood pressures in Tables 1 and 2 represent the average of all those taken during the period in which biological half-life was being determined. The average pressure of the hypertensive patients was significantly higher ($P < 0.01$) than that of the normotensive subjects in both studies.

**Administration and Counting of Isotope**

The source, chemical form, and purity of the $^{22}Na$ were as previously described (1, 2). Each subject was given approximately 1.5 to 3 μCi $^{22}Na$ (physical half-life = 2.6 years) orally as $^{22}NaCl$ with 1 to 2 mEq of NaCl as carrier dissolved in about 100 ml water in a beaker that was subse-
SODIUM$^{22}$ IN HYPERTENSION

On a daily intake of 5.3 g NaCl (biological half-life approximately 20 days), the total rad from 3 μc of this isotope was estimated to be approximately 0.10 (10). Radioactivity was counted when the subject was in the whole-body counter at least 10 to 14 times, either on consecutive or alternate days. The counts obtained were corrected both for background and for physical decay of the isotope. The counting technique and instrumentation were as described previously (1, 2), except that the tube-wired pulse-height analyzer used in earlier studies was replaced by a 400-channel transistorized gamma spectrometer. Also, while Study 2 was in progress a larger crystal was installed in the counter, which permitted the amount of $^{22}$Na to be reduced routinely to approximately 1.5 μc. Over a period of 8 weeks on a 5.3-g NaCl daily intake it was noted that the net whole-body counts/min for the $^{22}$Na decreased in simple exponential fashion when plotted against elapsed time. Accordingly, a plot of the logarithm of the net whole-body counts/min versus the time in days yielded a straight line, and from the slope of this line the biological half-life of $^{22}$Na was obtained. The line was fitted and the slope determined by the method of least squares, utilizing a program for the IBM 7094 digital computer. In all instances the significance of the difference between mean values of two groups was estimated using Student's $t$ test; only $P$ values $< 0.05$ were considered to have probable significance.

**Results**

Tables 1 and 2 summarize the pertinent data from these studies. In brief, whether the patients were given 5 or 10 g of added NaCl daily, the biological half-life of $^{22}$Na in them was not significantly different from that of normotensive subjects. The biological half-life of $^{22}$Na for the two levels of salt intake demonstrates that there was no consistent relationship between blood pressure and biological half-life of $^{22}$Na (Fig. 1). Attempts to correlate the biological half-life of $^{22}$Na with sex, age, weight, or duration of hypertension revealed no obvious trends.

**Discussion**

The present work fails to confirm our 1962 report that the biological half-life of $^{22}$Na was...
significantly longer in hypertensive subjects
than in normotensive subjects on the same
steady-state regimen (1, 2). In the earlier
work, the $^{22}$Na decay curves from which bio-
logical half-life was determined were fitted
by eye; in the present study they were fitted
by the method of least squares. The latter
method is less subject to error than the former
and this seemed initially to explain the dis-
parity between the earlier report and the
present studies. However, when the curves
from the previous study were refitted by the
method of least squares, the statistically sig-
nificant difference between hypertensive and
normotensive subjects disappeared for the in-
dividuals given 5 g added NaCl but remained
for those given 2 and 10 g added NaCl.
Therefore, the most likely explanation for the
differences in biological half-life observed in
the 1962 study is that with the small number
of subjects tested, there was a fortuitous selec-
tion of normotensive subjects with shorter bio-
llogical half-life for $^{22}$Na than prevailed among
the hypertensive patients. This view is sup-
ported by the following: the elimination of 1
normotensive subject (W. McD.) in Study 1
(Table 1) and of 2 normotensive subjects
(V. C. and A. K.) in Study 2 (Table 2) would
result in statistically significant differences
($P < 0.05$) between hypertensive and normo-
tensive subjects in the present study. Hence, a
more elaborate explanation seems unnecessary
at this time.

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*Circ Res.* 1966;19:750-754
doi: 10.1161/01.RES.19.4.750

*Circulation Research* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7330. Online ISSN: 1524-4371

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