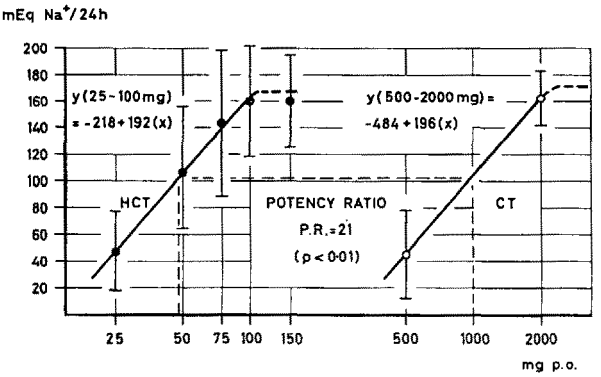
Natriuretic Potency of Hydrochlorothiazide[1] in Humans

Due to marked species differences, the therapeutic effectiveness of new diuretic agents can be estimated by clinical trial only. To eliminate subjective errors methods for human bioassay have been developed using a diuretic of known potency as a reference and body weight decrease in 24 h[2] or increase in daily sodium excretion as an index of diuretic potency[3]. If the dose of chlorothiazide[4], a non mercurial diuretic[5] is plotted on a logarithmic scale, a straight dose-response curve is obtained from 500 to 2000 mg[3]. Recently a new diuretic sulfonamide with similar structure[6], hydrochlorothiazide, has become available. Acute experiments in dogs and rats have shown it to be 4 to 16 times as potent as chlorothiazide[7]. Preliminary to clinical trials it was necessary to establish the potency of this new drug in humans.



Dose-response curves for hydrochlorothiazide (HCT) and chlorothiazide (CT) in humans (mean and standard deviation)

Ten patients suffering from mild right ventricular failure due to hypertensive or coronary heart disease, who needed at least intermittent diuretic therapy, were put on a diet with a constant sodium intake between 80 and 110 mEq/day. Sodium excretion during the control period varied between 70 and 105 mEq/day averageing 97 mEq/24 h. At 3 to 5 day intervals these patients received single doses of 25 (9 = number of assays), 50 (9), 75 (9), 100 (5), and 150 (5) mg of hydrochlorothiazide or 500 (5), 1000 (5), and 2000 (5) mg of chlorothiazide at 7 a.m. 24-h urines were collected and sodium excretion determined by flame photometry. Natriuretic potency was estimated by subtracting the average daily sodium excretion (97 mEq/day) from the individual responses.

The average increment in sodium excretion (mean and standard deviation) at different dose levels is shown in the Figure. If the doses are plotted on a logarithmic scale a straight dose-response curve is obtained between 25 and 75 (or 100) mg of hydrochlorothiazide and 500 and 2000 mg of chlorothiazide. 75 to 100 mg of hydrochlorothiazide induce a maximal response which cannot be further increased by additional amounts of the drug. For chlorothiazide the maximal response has been shown to occur with 2000 mg and, similar to hydrochlorothiazide, no further increase in natriuresis was noted with larger doses[3]. The potency ratio of hydrochlorothiazide to chlorothiazide as evaluated graphically (---) in the Figure is 21. Using the method of LITCHFIELD and WILCOXON[8] and 163 mEq increase in sodium excretion as a 100% response, it can be shown that the potency ratio for a 19/20 probability is 16 with confidence limits from 8 to 31. A detailed report of these experiments will be presented elsewhere[9].

From a physiological viewpoint it is interesting that the maximal response obtained with any dose of chlorothiazide and hydrochlorothiazide is quantitatively and qualitatively (electrolyte pattern in acute experiments in humans[9]) identical though hydrochlorothiazide is about 20 times as active as chlorothiazide. This probably means that both drugs inhibit sodium reabsorption at the same site and by the same mechanism of action. Enzymatic conversion of chlorothiazide to hydrochlorothiazide *in vivo*, similar to the hydrogenation of some steroid hormones might explain the discrepancy in diuretic effectiveness.

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Zusammenfassung

Hydrochlorothiazide[1], ein oral verabreichbares Diuretikum, führt beim Menschen in Dosen von 25 bis 75 mg zu einer exponentiellen Zunahme der Natriumausscheidung. Eine maximale Diurese wird mit 75–100 mg erreicht. Das neue Pharmakon ist 20mal aktiver als Chlorothiazide[4].

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Depolarizing Action of K-Strophantine and K-Strophantoside on Isolated Frog Skin

In past years many authors have worked on the potential in isolated frog skin using various drugs.

The action on the skin potential and water transport was studied with pitressin (CAPRARO and BERNINI[1], SAWYER[2], CAPRARO and TIENGO[3], BRAUN[4], KOEFOED-JOHNSEN and USSING[5]), epinephrine (USSING[6], CAPRARO and TIENGO[3], CAPRARO and FRANCESCHINI[7]), and some enzymatic inhibitors (i.e. acetazolamide: FUHRMAN[8], HUF *et al.*[9]), and more recently with serotonin (PICKLES[10]), Mersalyl, and theophylline (HUF *et al.*[9]).

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