Spironolactone: Relationship between Concentrations of Dethioacetylated Metabolite in Human Serum and Milk

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Abstract □ The concentration of canrenone, a principal metabolite of spironolactone, was determined in human serum and milk. The milk to serum concentration ratios of this metabolite were 0.72 at 2 hr and 0.51 at 14.5 hr after ingestion of spironolactone. It was estimated that the maximum quantity of canrenone ingested daily by a human infant *via* its mother's milk would be approximately 0.2% of the daily dose of spironolactone given to the mother.

Keyphrases □ Spironolactone metabolite—canrenone, human milk to serum concentration ratio □ Canrenone—human milk to serum concentration ratio □ Aldosterone antagonists—canrenone, human milk to serum concentration ratio

Excretion of drugs and/or their biologically active metabolites in human milk in amounts sufficient to elicit pharmacological responses in the nursing infant is a potential risk associated with numerous drugs (1). High lipid solubility, nonionization at blood pH, and low binding to plasma proteins are some factors that favor drug transfer from blood to milk. Several reviews (2–4) documented excretion of various classes of drug molecules in human milk; however, for spironolactone[1], no information is available regarding milk excretion of either the unchanged drug or its metabolites.

Previous studies showed that spironolactone is rapidly and extensively metabolized in humans. The unchanged drug has not been detected in the urine (5–8). The principal metabolite in the blood is the dethioacetylated derivative, canrenone[2], which is extensively (98%) bound to plasma proteins and has a log-linear phase half-life of about 17 hr (8). Recently, the single oral dose of canrenone was reported to have about one-third the activity of spironolactone in inhibiting the action of fludrocortisone on electrolyte elimination in humans (9). This paper reports findings on the relationship between the concentration of canrenone in human serum and milk.

EXPERIMENTAL

A 28-year-old primagravida Caucasian patient with documented primary hyperaldosteronism took 25 mg of spironolactone twice a day until the spontaneous onset of labor at 37 weeks gestation, resulting in the normal delivery of a healthy female infant (2.69 kg). Breast feeding was permitted, and the infant's serum electrolytes were monitored. Seventeen days after birth, the mother's blood and expressed breast milk specimens were taken in the morning, 14.5 hr after her last 25-mg dose. (The dosage by that time had been increased to 25 mg four times a day.) The mother took her first dose of the day, and 2 hr later (after nursing) the maternal blood and expressed milk specimens were again obtained. Serum was separated within 30 min of collection, and biological specimens were stored at −20° until analysis.

Canrenone levels were assayed by the spectrofluorometric method of Gochman and Gantt (5). Since this method does not describe canrenone measurement in milk, initial recovery studies were performed after known amounts of canrenone were added to the control milk of a healthy mother. In the concentration range of 50–400 ng/ml, the recovery was between 95 and 115% and the coefficient of variation ($n = 3$) was less than 14%. For a 1-ml sample, the lowest limit of detection was 25 ng/ml.

RESULTS

At 2 hr after ingestion of spironolactone (25 mg), the serum and milk concentrations of canrenone (average ± *SD* of three determinations) were 144 ± 8 and 104 ± 4 ng/ml, respectively. At 14.5 hr, the corresponding values were 92 ± 4 and 47 ± 3 ng/ml. The milk to serum concentration ratios at early and late periods were 0.72 and 0.51, respectively, indicating that the canrenone concentration in the milk declined at a rate similar to that in the serum.

DISCUSSION

Canrenone is a lipid-soluble steroid and exists in the unionized form in the blood. These factors tend to favor its transfer from blood to milk. The low milk concentration of canrenone in the present study can be attributed to its extensive binding to the plasma proteins (8). Karim *et al.* (10) found that the maximum and minimum steady-state plasma levels of canrenone in healthy males who received twice the usual recommended doses of spironolactone (200 mg once a day) were approximately 500 and 100 ng/ml, respectively.

If it is assumed that the milk to serum (or plasma) concentration ratio of canrenone is 0.8 and that the infant's breast milk intake per day is 1000 ml, then the maximum quantity of canrenone that could be ingested by the infant per day would be about 0.2% of the mother's daily dose of spironolactone. In the present study, serum levels of sodium and potassium were monitored in the infant and were in the normal range. In this case, the amount of canrenone excreted in milk while the mother was receiving therapeutic doses of spironolactone was not clinically significant. However, nursing infants of treated mothers should have their electrolyte balance monitored (serum and urine) until additional data can be collected to allow for possible biological variation.

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[1] Aldactone, G. D. Searle & Co., is 17β-hydroxy-7α-acetylthio-3-oxopregn-4-ene-21-carboxylic acid γ-lactone.

[2] Also known as Aldadiene, Phanurane, and SC-9376 and is 17β-hydroxy-3-oxopregna-4,6-diene-21-carboxylic acid γ-lactone.