VOLUME 2

Therapeutic DRUGS

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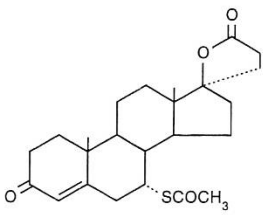
Spironolactone

Spironolactone is probably the most important steroidal lactone in clinical use; it acts as a diuretic and antihypertensive agent by antagonizing the sodium-retaining effects of aldosterone, and also in part by inhibiting the adrenocortical biosynthesis of aldosterone.

Chemistry

Spironolactone (Aldactone, Diatensec, Spiroctan, Spirolone)
$C_{24}H_{32}O_4S$
7-α-Acetyl-thio-3-oxo-17α-pregn-4-ene-21-17β-carbolactone acid-γ-lactone



Molecular weight	416.1
pKa	not relevant
Solubility	
in alcohol	1 in 80
in water	insoluble
Octanol/water partition coefficient	—

Spironolactone is a white to light tan powder with a slightly bitter taste and is usually odourless or has a slight odour of thioacetic acid. It is prepared by chemical synthesis.

Spironolactone is also available in oral combination with frusemide (Lasilactone = frusemide 20 mg and spironolactone 50 mg) and with hydroflumethiazide (Aldactide 25 = hydroflumethiazide 25 mg and spironolactone 25 mg).

Pharmacology

The antimineralocorticoid properties of the spirolactones were first recognized more than 30 years ago.[1] Spironolactone is a competitive inhibitor of the binding of aldosterone to its receptor. Its most important site of action is the distal portion of renal tubules where it combines with soluble cytoplasmic aldosterone receptors to form complexes which are inactive and which do not bind to nuclear-acceptor sites, thus preventing a chain of biochemical events leading to the synthesis of physiologically active proteins.[2,3] Thus it promotes a diuresis and acts as an antihypertensive agent. Administration of spironolactone is associated with reversal of the electrolytic changes attributed to aldosterone and with a dose-dependent increase in plasma renin activity in rats.[4]

A separate but less important effect is direct inhibition of adrenal synthesis of aldosterone.[5]

Toxicology

The acute toxicity of spironolactone is low in rats, mice and rabbits, so that there is a high potential therapeutic ratio.

During chronic testing histological changes were noted in rat liver, thyroid gland and male genitalia. There were also changes in monkey testes and male mammary glands. In a 78-week study in rats, a number of malignant tumours occurred, mainly affecting skin and with a control group it was not clear that the incidence of tumours was greater than would be expected in any ageing rat population. Thus, whether spironolactone predisposes to tumour formation remains an unresolved question.[6]

Clinical pharmacology

Spironolactone is a competitive inhibitor of aldosterone through binding at receptor sites, the most important of which lie in the late distal renal tubules and the renal collecting system. Thus urinary sodium and water loss and retention of potassium and hydrogen result and the clinical effects are a diuresis and lowering of blood pressure.[7]

Spironolactone also inhibits adrenocortical aldosterone biosynthesis in patients with primary hyperaldosteronism, of which 'spironolactone bodies' identified in the adrenal tumour cells of treated patients are thought to be a morphological expression.[8] Theoretically, such a mechanism could enhance diuretic activity but its therapeutic importance is uncertain.

Spironolactone is primarily useful as a diuretic in patients with hyperaldosteronism. Thus it is effective in patients with ascites due to liver failure, and in patients with resistant heart failure (i.e. where other diuretics have failed). It is less useful as a first-line diuretic. Its antihypertensive effects are relatively modest in essential hypertension but it is of value in the treatment of hypertension due to primary hyperaldosteronism where other definitive treatments (e.g. surgery) are not feasible.

Single-dose studies in normal volunteers in the range 50–800 mg produced a dose-dependent reversal of aldosterone-induced sodium retention and/or decrease in the plasma Na/K ratio.[9] In essential hypertension no difference in antihypertensive effect was found between daily doses of 100, 200 or 400 mg[10] and a maximum dose of 75–100 mg per day has been recommended.[11] However, there was a dose relationship with plasma sodium, potassium and weight.[10] By comparison, spironolactone in doses of up to 400 mg per day may be necessary in the treatment of primary hyperaldosteronism.[7,12] Because of the prolonged duration of activity of its metabolites, spironolactone may be administered in a single daily dose.

Spironolactone causes a number of electrolyte changes, notably a reduction in plasma sodium and bicarbonate, together with dose-dependent elevations in plasma renin, potassium and creatinine. Fasting blood sugar, cholesterol and triglycerides are not significantly affected.[11,13]

Spironolactone was thought to increase calcium excretion through a direct effect on tubular transport, but this was later refuted.[14]

Pharmacokinetics

In the past spironolactone has been assayed using a spectrophotofluorimetric method[15] but now a HPLC assay is in more common use which has a sensitivity[16,17] of 5 $\mu g.l^{-1}$. However, because the drug is extensively metabolized to canrenone and other metabolites which are also competitive antagonists of aldosterone, pharmacokinetic studies focus on the metabolic pathways.

Oral absorption of spironolactone is variable because of its low aqueous solubility. In rhesus monkeys almost complete absorption of the drug was obtained from an aqueous ethanolic solution, and in man, absorption is enhanced by micronization of the drug in the tablet.[18,19] There is improved absorption if the drug is taken after food, probably because by delaying gastric emptying, food promotes disintegration of the tablet and improves dissolution of the drug.

Furthermore, bile acids secreted in response to the meal may dissolve spironolactone, which is very lipophilic.[20] The peak plasma concentration was observed at 1 hour in normal volunteers after a standardized meal. Systemic bioavailability has been estimated at 60–70% and the plasma half life is 1.3 ± 0.3 (SD) hours. The drug can still be detected up to 8 hours after ingestion but it is extensively metabolized so that the free drug is not detected in urine.[21–23]

Spironolactone is 98% protein bound but its volume of distribution is unknown.[24] The extent of tissue accumulation of the drug and its ability to cross the blood–brain barrier are not known. In lactating women taking spironolactone, levels of canrenone in milk were low and it was estimated that the maximum quantity of canrenone ingested daily by the human infant via milk was 0.2% of the maternal daily dose of spironolactone.[25]