

natremia can be avoided and successfully treated with proper monitoring of electrolytes and hydration of patients.

Actions

A10 is a differentiation-inducing agent. The mechanism of the induction of terminal differentiation by A10 is unknown. It is postulated that abnormal cells under the influence of A10 transform into differentiating cells that ultimately enter the phase of irreversible senescence and cell death. When all cancerous or abnormal cells undergo differentiation and programmed cell death, the patient enters remission.

The basic mechanism of A10 seems to be the substitution of glutamine by PG. The relative excess of glutamine is essential for a cell entering the S phase of the cell cycle and cell division. Availability of glutamine to cells in the human organism is regulated through the well-known conjugation of glutamine with phenylacetic acid into PG. More than 90% of PN is bound with glutamine to form PG. Administration of A10 to patients introduces PG, which competes with glutamine. Isoglutamine and its derivatives have shown marked antitumor activity in tissue culture studies. The conditions after administration of A10 favor cellular differentiation and inhibition of neoplastic cell growth.

Antineoplaston AS2-1 is a gene-regulating and differentiation-inducing agent. The active ingredient of AS2-1, PN, is known to modulate the expression of *ras* oncogenes and tumor suppressor gene p53 (see "Biologic Mechanism of Action").

Pharmacokinetics

In patients with neoplastic disease, rapid A10 infusions produce plasma PG levels in the range required for in vitro antineoplastic activity. In these patients, A10 is rapidly cleared from plasma and PG and isoPG levels in plasma near preinfusion levels within 4 hours of infusion. Animal studies have shown that within 4 hours of drug administration, approximately 70% of the A10 is excreted in the urine in an unaltered form.

Oral AS2-1 in humans (22.0 to 36.0 mg/kg) produces a rapid (30 to 120 minutes) and dose-dependent increase in plasma PN levels that peak at 1.0 to 2.0 mmol. Patients receiving AS2-1 injections (total phenylacetate in ~10-min injections = 0.23 mmol/kg) immediately after A10 injection have mean peak plasma PN levels near 3.0 mmol. These levels are similar to levels required for in vitro antineoplastic activity. With both oral and intravenous treatment, plasma PN levels return to preinfusion levels 4 to 5 hours after drug administration. At this point, tissue levels of PN are highest in liver and kidney. In humans, 99% of infused PN is excreted in the urine as the glutamine conjugated form (for example, as PG).

Warnings, Contraindications, and Precautions

Serious hypernatremia was observed in 10 of 1216 cases (0.8%); however, only 3 cases were not resolved. One patient refused the treatment, and in two additional cases, hypernatremia was a premortal event for patients with terminal brain tumors. One of these patients died