Toxicity studies with acyclovir sodium in mice

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Abstract

Acyclovir sodium was injected in mice in daily doses of 15 mg/kg (Gp I), 30 mg/Kg (Gp II) and 60 mg/Kg (Gp III) respectively. Mortality occurred in the Gp I and Gp II mice in the 4th week. Gp III animals died at regular intervals after day 5.

Acyclovir caused decrease in food consumption and body weight and also depression of C.N.S. in proportion to the dose administered. Isolated cases of alopecia, hemiplegia and dermatitis occurred.

Acyclovir in doses of 15 mg/Kg and 30 mg/Kg was well tolerated up to 3 weeks of daily drug administration. A dose of 60 mg/Kg was found to be toxic in mice.

Keywords: Acyclovir; mice; injectible; toxicity; mortality.

Introduction

Infections with HIV and herpes simplex virus (HSV) are a major and increasing cause of morbidity in many countries.[1] Acyclovir is highly effective against genital HSV, and fairly effective against HIV.[2] The parenteral form of acyclovir has been effective in the treatment of disseminated herpes infection[3], and vericella zoster[4] in immunocompromised patients.

Although acyclovir has been reported to be relatively safer, adverse effects such as nausea, vomiting, rash, rigors, hypotension, decreased renal function and pain or local reactions at the injection site[5], dizziness, transient rise in blood urea and creatinine have been reported.[6]

On the other hand, the use of oral acyclovir was not associated with any hepatic, renal or neurological toxicity.[7]

Since acyclovir is administered for long durations, we thought it worthwhile to conduct acute and subacute toxicity studies with injectible acyclovir in mice.

Materials and methods

Twenty-four mice of either sex, weighing 20-30 g., were divided into four groups of six mice each. Acyclovir sodium powder for injection was supplied by M/S Torrent Pharmaceuticals Ltd. The powder was dissolved in normal saline. The drug was injected I.V., through tail veins, twice a day in total dose of 15 mg/kg/day (Gp I), 30 mg/kg/day (Gp II), and 60 mg/kg/day (Gp III) respectively, in all the three groups for 20 days.

The fourth group of six mice served as control (Gp IV) and the mice were injected 0.25 ml. of normal saline twice daily for the study period, i.e., 28 days.

Animals were kept in separate metabolic cages under similar housing conditions. In case of death, the dead animals were replaced with new ones. Animals were observed from the point of view of a number of parameters.

Results were analysed by the 'Z' test for proportion.

Results

No mortality occurred with doses of 15 mg/kg/day and 30 mg/kg/day till the third week of daily drug administration. However, during the fourth week, 2 and 3 animals died in Gp I and Gp II respectively. In Gp III, there was no mortality up to the 5th day of administration, but subsequently the animals died at regular intervals.

It may be observed that the drug is well tolerated in doses of 15 and 30 mg/kg up to three weeks of daily administration.

Acyclovir caused dose-dependent decrease in body weight at all the three dose levels, which could be attributed to decrease in appetite following acyclovir. Decrease in food consumption was observed and was in proportion to the dose of acyclovir.

A characteristic balding pattern was visible in all the three acyclovir-treated groups. Fall of hair started from the nape of neck and extended towards tail, on the dorsal surface of the body. This alopecia appeared earliest and was most extensive in Gp III and was last to appear and minimum in Gp I mice.

All the mice treated with acyclovir showed dose-dependent signs of central nervous system (C.N.S.) depression in proportion to the dose administered.

Motility, probing, pinna reflex, sound reflex, and righting reflex were decreased in proportion to the dose of acyclovir. Activity measured by Animex activity meter also decreased in a dose-dependent fashion.

No animal showed signs of C.N.S. excitation.

Left-sided hemiparesis occurred in one animal of Gp II on day 13. Left-sided hemiparesis with twisting of neck and face towards the left occurred in another animal of Gp II on day 17.

Paraplegia occurred on day 15 in one animal of Gp III.

Dermatitis was observed at the site of injection in one male mouse at a dose of 15 mg/kg/day.

Peeling of skin occurred in cases of subcutaneous spilling of drug.

No gross abnormality was detected in any organ of mice in all three groups.

Table I: Effect of intravenous Acyclovir (ACL) Administration on the body weight and food consumption of mice. (Data are mean ą s.e.m.)

	DAYS						
Group	Day 1	Day 5	Day 10	Day 15	Day 20	Day 24	Day 28
Control (n=6)							
Body weight (g)	25.50ą0.70	26.1ą0.41	26.8ą0.34	26.4ą0.90	27.1ą0.63	27.5ą0.77	27.8ą0.62
Food Consumption (g)	5.36ą0.01	5.45ą0.02	5.75ą0.04	5.60ą0.06	5.70ą0.04	6.00ą0.03	6.10ą0.02
Group II (ACL 15 mg/kg) (n=6)							
Body weight (g)	23.60ą0.64	* 23.1ą0.76	** 22.50ą0.81	** 22.30ą0.70	*** 21.50ą0.42	*** 19.80ą0.36	*** 18.20ą0.54
Food Consumption (g)	5.40ą0.01	** 5.00ą0.04	4.60ą0.05	*** 4.30ą0.03	*** 4.00ą0.02	*** 3.60ą0.01	*** 3.00ą0.04
Group II (ACL 30 mg/kg) (n=6)							
Body weight (g)	24.50ą0.44	* 23.80ą0.60	* 23.00ą0.12	** 22.00ą0.81	*** 21.10ą0.46	*** 20.00ą0.06	–
Food Consumption (g)	5.50ą0.05	*** 4.70ą0.03	4.10ą0.02	*** 3.50ą0.02	*** 3.00ą0.01	*** 2.50ą0.06	–

Group III (ACL 60 mg/kg) (n=6)							
Body weight (g)	23.80ą0.23	* 22.60ą0.43	*** 20.10ą0.52	*** 18.50ą0.41	–	–	–
Food Consumption (g)	5.40ą0.02	*** 4.50ą0.02	3.50ą0.06	*** 2.50ą0.07	–	–	–

* p<0.05, ** p<0.01, *** p<0.001, vs control

Table II: Effect of different doses of acyclovir (i.v.) on the gross and fine movements of mice.

(Data are mean ą s.e.m.)

DAYS							
Group	Day 1	Day 5	Day 10	Day 15	Day 20	Day 24	Day 28
Control (n=6)							
Gross activity score	2066.01ą 41.27	2138.83ą 37.58	2446.83ą 28.96	1964.33ą 39.52	1986.16ą 57.12	2172.16ą 61.34	2124.83ą 48.42
Fine activity score	1019.33ą 38.46	1230.83ą 51.28	1246.53ą 46.48	1103.41ą 59.52	1024.08ą 60.71	1310.66ą 57.29	1082.68ą 42.28
Group A (ACL 15 mg/kg) (n=6)							
Gross activity score	24.65.56ą 72.68	* 1761.83ą 67.78	*** 910.66ą 44.12	*** 862.33ą 58.74	*** 602.33ą 61.38	*** 567.28ą 71.21	*** 411.25ą 87.12
Fine activity score	962.71ą 46.49	** 876.66ą 51.49	*** 666.83ą 48.16	*** 518.06ą 62.28	*** 499.66ą 57.72	*** 319.27ą 38.78	*** 249.44ą 49.86
Group B (ACL 30 mg/kg) (n=6)							
Gross activity score	2030.66ą 89.72	** 1090.52ą 72.70	*** 678.83ą 89.10	*** 454.81ą 67.43	*** 358.54ą 46.51	*** 212.75ą 36.61	–
Fine activity score	967.83ą 72.30	746.16ą 57.64	568.83ą 55.48	*** 399.86ą 63.78	*** 241.75ą 48.63	*** 149.55ą 37.63	–
Group C (ACL 60 mg/kg) (n=6)							

Gross activity score	1829.16ą 31.70	*** 500.16ą 44.62	*** 315.50ą 39.78	*** 216.07ą 73.63	–	–	–
Fine activity score	958.53ą 40.80	405.57ą 77.61	235.75ą 81.08	*** 178.54ą 76.21	–	–	–

* p<0.05, ** p<0.01, *** p<0.001, vs control

Discussion

A drug like acyclovir should be judged with special care for carcinogenic and mutagenic potentials. Although acyclovir is mainly incorporated in viral genome, very high doses have also shown genotoxic effects in mammalian cell systems.[8] However, this manifestation does not appear to represent a potential hazard.[9] In general, acyclovir seems to have a low toxic potential, especially in animal models.[10,11,12] In man, acyclovir has plasma half life of approximately three hours; is widely distributed throughout the body tissues, and is rapidly cleared, mainly as unchanged drug, through kidneys.[13]

In the present study, injected acyclovir was well tolerated by mice in low and moderate doses and showed toxic manifestations in very high doses of 60 mg/kg/day only. Corresponding doses, especially high doses are not likely to be used in humans, but still, it has to be administered with caution.

Conclusion

Acyclovir seems to have a low toxic potential in mice. Data from available observations and investigations do not give support for a mutagen, teratogen or carcinogen hazard in patients receiving recommended clinical doses.[8] An awareness for a potential risk for the foetus, especially with infusion treatment should nevertheless be kept in mind.

The possibility of toxic hazards in foetus, even in low doses, should be taken into account.

It can be concluded that acyclovir administered to mice in low doses of 15 mg/kg/day and moderate doses of 30 mg/kg/day was well tolerated up to 3 weeks of daily drug administration. However, a high dose of 60 mg/kg/day was found to be toxic in mice.

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