Possible Protective Role Of Erythropoietin In Vincristine-Induced Central Toxicity in Rat

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Introduction

- Vincristine (VCR) is an antineoplastic agent that is used in several leukemia patients treatment protocols.[1]
- VCR has serious neurological side effects that ranges from peripheral neuropathy to seizures.[2]
- VCR central toxicity is attributed to the SIADH secretion which results in hyponatremia and seizures. [2]
- Cytochrome P450 inhibitors including oral azole antifungals were shown to increase the VCR central toxicity. [2]
- Erythropoietin, a renal glycoprotein hormone, is commonly used in treatment of anemia and decreases blood transfusions in leukemic patients. It was also shown to affect the sodium and potassium levels. [3]
- Hypersecretion of ADH was associated with an increase in erythropoietin secretion. Erythropoietin was also found to have a reversal role against vincristine-induced neuropathy probably through decreasing N-methyl-D-aspartate receptor expression and increasing calcitonin gene-related peptide expression centrally and peripherally. [4]

Objective

1. To develop a rat model to study vincristine-induced SAIDH
2. To determine the possible role of erythropoietin in reducing the hyponatremia and survival rate associated with vincristine-induced SAIDH

Methods

- Male Sprague-Dawley rats were allocated into five groups (n=4-8 each).

All rats received 0.15 ug/Kg (I.P.) vincristine sulphate for 15 days /6 days per week

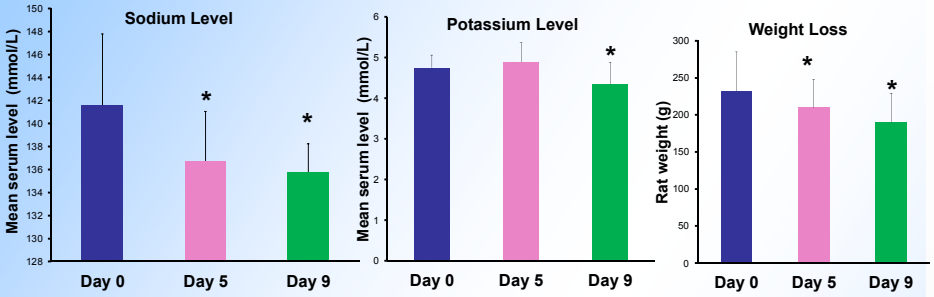
- GpI: Model development group injected VCR only
- GpII: administered 40U/Kg erythropoietin i.p. along with the VCR.
- GpIII: administered 80U/Kg erythropoietin i.p. along with the VCR.
- GpIV: administered 40 mg/Kg posaconazole (PSZ) orally starting the day of VCR administration
- GpV: administered 80U/Kg erythropoietin i.p. and 40 mg/Kg posaconazole (PSZ) p.o. starting the day of VCR administration.

1. Blood Sampling at days 0, 5, 9 and 15 and sodium and potassium levels were measured
2. Rats' weights and survival rates were measured daily

Results

- Most of the treated rats did not survive after day 12 of dosing.

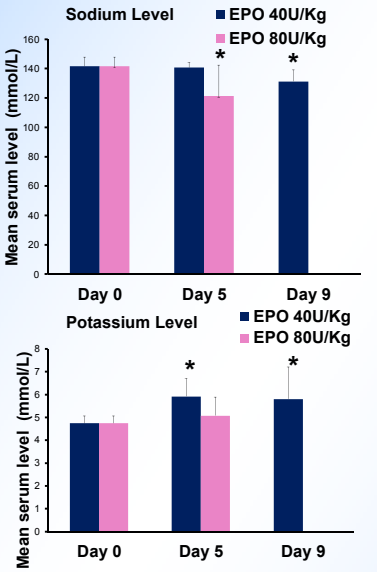
Group I: Model development



The VCR-induced SAIDH rat model
- showed 3.4 % and 4.1% reduced sodium levels on days 5 & 9, respectively.
- serum potassium level showed no significant change on day 5 and 8% decrease on day 9.
- The rats exhibited weight reduction of 10% and 18% on days 5 and 9, respectively.

*Significantly different from day zero ($p<0.05$)

Groups II & III: Erythropoietin treated rats



Erythropoietin 40 U/Kg treated rats showed
- Significantly less hyponatremia, 0.6% decrease only, and 24% increase in potassium levels on day 5.
- Increasing the erythropoietin therapy duration beyond 5 days resulted in potentiating the hyponatremic effect of VCR (7.3% decrease at the 9th day)

Erythropoietin 80U/Kg treated rats showed
- increased hyponatremia
- elevated potassium levels
- demolished rats' survival rates

* denotes different from day zero in the same dose-treatment group ($p<0.05$)

Groups IV & V: Posaonazole treated rats

- Posaconazole treated rats did not survive beyond day 4 of treatment.
- Posaconazole-VCR treated groups showed increased VCR toxicity with ~12% increase in serum potassium levels, however, serum sodium levels showed no significant difference during the 4 days.

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Conclusions:

Initial rat model to study vincristine-induced SAIDH was developed. Co-administration of low dose erythropoietin (40 U/Kg) for short duration, ≤5 days, showed a potential benefit in reversing the VCR-induced hyponatremia however, we need to consider controlling the induced hyperkalemia. Human serum sodium, potassium and BUN levels for patients administered VCR alone or VCR along with erythropoietin in Acute lymphoblastic leukemia (ALL) treatment protocols needs to be studied to confirm such trends.

Future Plans:

A retrospective or a prospective study needs to be pursued to check for human serum sodium, potassium and BUN levels for patients administered VCR alone or VCR along with erythropoietin in ALL treatment protocols to confirm such trends.

References
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