Voriconazole Individual Project Outline - Jiaqi Fu

Prompt:

Is your drug expected to be safe and effective in a special population of pharmacogenetically variant(2E) patients?

> **I want to investigate how the pharmacogenetic variant of the CYP enzyme will affect the ADMET of a 6-year-old boy who was infected by fungus and needs to be treated with Voriconazole(orally).**

Steps:

1. **Therapeutic Window for Voriconazole:**

   A study that was published in 2008 implemented therapeutic drug monitoring on Voriconazole - a total of 181 measurements were performed in 52 patients, revealing the large variability of concentration in the blood. 25% of measurements showed low dose levels (n <= 1mg/L), and 1mg/L was considered to be the lowest effective dose level; while 31% of measurements showed high dose levels (n > 5.5mg/L), and dose level higher than 5.5mg/L will cause potential toxicity. [1]

2. **Create a pediatric physiology by creating a new PEAR population with selected pediatric demographics:**

   According to the CDC, the average height of a 6-year-old boy is 115.6 cm and weight is 21.7kg.[2]

Age	Height Females in Inches	Height Males in Inches	Weight Females in Pounds	Weight Males in Pounds
1	27 to 31	28 to 32	15 to 20	17 to 21
2	31.5 to 36	32 to 37	22 to 32	24 to 34
3	34.5 to 40	35.5 to 40.5	26 to 38	26 to 38
4	37 to 42.5	37.5 to 43	28 to 44	30 to 44
6	42 to 49	42 to 49	36 to 60	36 to 60
8	47 to 54	47 to 54	44 to 80	46 to 78
10	50 to 59	50.5 to 59	54 to 106	54 to 102
12	55 to 64	54 to 63.5	68 to 136	66 to 130
14	59 to 67.5	59 to 69.5	84 to 160	84 to 160
16	60 to 68	63 to 73	94 to 172	104 to 186
18	60 to 68.5	65 to 74	100 to 178	116 to 202

3. **Apply the best Voriconazole Oral Model on the new PEAR physiology, and then change the Vmax of CYP enzymes to mimic different gene expression levels. Trace the concentration of the drug in arterial blood to observe if it falls in the therapeutic window. Investigate how the genetic variants of the CYP enzymes will affect ADMET.**

Hypothesis:

Voriconazole will be safe and effective in the 6-year-old-child population group with CYP2C19 and CYP3A4 variants.

Reference:

1. Pascual, A. *et al.* Voriconazole Therapeutic Drug Monitoring in Patients with Invasive Mycoses Improves Efficacy and Safety Outcomes. *Clin. Infect. Dis.* **46**, 201–211 (2008).
2. Normal Growth | Childhood Development. https://www.cincinnatichildrens.org/health/g/normal-growth.