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Favipiravir for children with Ebola

Epidemiological data from UNICEF Guinea[1] showed that children have accounted for a substantial proportion of patients admitted to west African medical centres for Ebola. 390 (22%) of 1744 reported patients infected with Ebola virus from the present outbreak in Guinea were children.[1] The overall case fatality proportion in the outbreak tends to be higher in children (73·4%) than in adults aged 15–44 years (70·8%).[2] In the context of an urgent need to assess potential specific interventions for Ebola in children, favipiravir is an interesting drug candidate because of its efficacy against Ebola virus in-vitro and animal models, good tolerance profile in adults, immediate availability, and ability to be used in the paediatric population because pills can be crushed and mixed with food and liquid. So far, there is no clinical experience of favipiravir use in children, making prediction of the optimum dose for Ebola difficult. However, the fact that maturation profiles of enzymes (mainly aldehyde oxydase) included in the metabolic pathway of favipiravir are fully achieved at the age of 12 months makes the drug a good candidate for treatment in children older than 1 year.[3]

We aim to explain the approach we used to propose a dosage regimen in an ongoing trial (NCT02329054) in Guinea assessing survival in children infected with Ebola and treated with favipiravir. We previously estimated that plasma daily minimal (Cmin) and average concentrations to be targeted in humans were 10 µg/mL and 113 µg/mL, respectively.[4] We used the pharmacokinetic model developed by the manufacturer with the parameter values (along with their estimated between-subject variability) estimated in healthy US adult volunteers to predict the disposition in paediatric patients, using weight-based allometric scaling. According to allometry theory, clearance, volume of distribution, and rate-constant parameters were scaled with a fixed exponent of 0·75, 1·0, and –0·25 respectively.[5] We then determined paediatric favipiravir doses according to bodyweight to reach a Cmin of more than 10 µg/mL without exceeding the predicted maximum concentration obtained in adults.[4] Because viral spread has to be blocked as soon and as strongly as possible after appearance of the first symptoms, several loading-dose strategies on day 1 were assessed by modelling to rapidly achieve high levels of exposure, and simulations were then done with various maintenance doses (table). Similar to adults, we suggest that children receive the treatment for 10 days, to reduce the risk of relapse. Tolerance, virological, and pharmacokinetic data will be collected in the trial to help refine the dosage regimen.

We declare no competing interests

	Day 1			Days 2 –10
	H_0 (first dose)	H_8	H_{16}	
10–15 kg	500 mg	500 mg	200 mg	200 mg three times daily
16–21 kg	800 mg	800 mg	400 mg	400 mg twice daily
22–35 kg	1200 mg	1200 mg	600 mg	600 mg twice daily
36–45 kg	1600 mg	1600 mg	800 mg	800 mg twice daily
46–55 kg	2000 mg	2000 mg	1000 mg	1000 mg twice daily
>55 kg (adults)	2400 mg	2400 mg	1200 mg	1200 mg twice daily

H=hour

Table: **Weight-band dosing table for faripiravir in children infected with Ebola virus disease**

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