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The tear production of tecovirimat in a single hospitalized mpox patient: a pharmacokinetic analysis

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Mpox is an orthopox DNA virus.[1,2] Ophthalmic manifestations include preseptal cellulitis, conjunctivitis and keratitis, either as a primary or secondary viral infection or a secondary bacterial infection.[2] Tecovirimat (Tpoxx) is an oral orthopox-specific drug that inhibits the orthopoxvirus VP37 envelope-wrapping protein and prevents the formation of egress-competent virions.[3] There are limited pharmacokinetic/pharmacodynamic (PK/PD) data available. We present a case report of a critically unwell mpox patient, who had tecovirimat PK sampling of plasma and tears.

A 30-year-old male was admitted to a local hospital in status epilepticus, 4 days after returning from Lagos, Nigeria. The patient had a history of traumatic brain injury and secondary epilepsy, for which he was on oral levetiracetam 750 mg twice daily. He had been given oral ciprofloxacin for secondary bacterial infection of presumed varicella zoster lesions prior to returning to the UK. The patient required intubation and ventilation in the management of his status epilepticus and developed compartment syndrome of his upper limbs, requiring bilateral fasciotomies. He developed acute kidney injury secondary to rhabdomyolysis (creatinine kinase >750 000 U/L) requiring continuous veno-venous haemofiltration (CVVHF). A skin lesion swab was positive for orthopox and mpox DNA on Day 3 of hospital admission. The patient was commenced on oral tecovirimat 600 mg twice daily for 14 days, crushed via nasogastric tube because IV tecovirimat was not available. The mpox clade was confirmed to be a novel clade 2b, lineage A.3 (IIb.A3).[4]

On Day 21 of hospitalization the patient complained of redness and mild discomfort in his right eye and was empirically commenced on topical chloramphenicol 1% ointment. On Day 36 the symptoms had worsened. Bedside review by an ophthalmologist with a portable slit lamp revealed a 6×11 mm ulcer involving mainly the inferior half of the cornea with no evident corneal stromal involvement (Figure 1). Corneal sensitivity was significantly reduced. The left eye examination was unremarkable. Ocular swabs were taken for microscopy, culture and sensitivity, plus mpox PCR. The swab results were positive for mpox DNA, likely secondary to autoinoculation from a hand lesion. The patient was restarted on oral tecovirimat 600 mg twice a day for a further 14 days and subsequently on 2-hourly topical trifluridine 1% drops for a total of 10 days. The patient was continued on trifluridine eye drops until he was discharged to the rehab unit. On Day 74 post admission, the corneal ulcer had greatly reduced to 0.6×4 mm, but there was now an inferior 2×6 mm crescent-shaped stromal haze. The patient remained only on

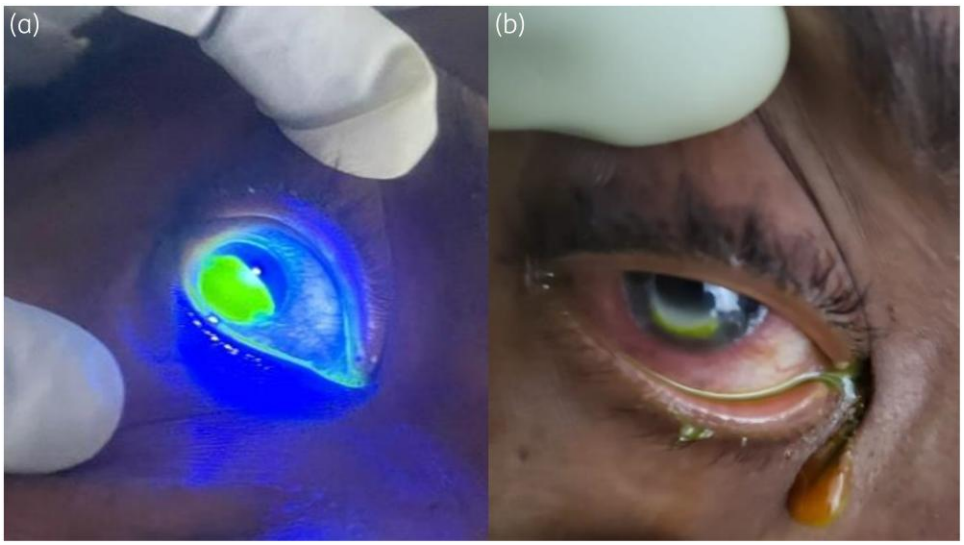

Figure 1. Progression of the patient's ophthalmic disease. (a) Day 36 initial presentation showing 6 mm × 11 mm inferior corneal ulcer with fluorescein staining. (b) Day 74 showing a healing corneal ulcer measuring 0.6 mm × 4.0 mm with a stromal infiltrate.

artificial tears. The patient's virology results are summarized in Table S1 (available as Supplementary data at *JAC* Online).

During the patient's acute severe phase of illness, a relative gave proxy consent for him to participate in the ISARIC WHO Clinical Characterisation Protocol for Severe Emerging Infection UK [the ISARIC WHO CCP-UK protocol; consent documents are available (open access) at https://isaric4c.net/protocols/]. Ethical approval was given by the South Central—Oxford C Research Ethics Committee in England (Ref 13/SC/0149), the Scotland A Research Ethics Committee (Ref 20/SS/0028), and the WHO Ethics Review Committee (RPC571 and RPC572, 25 April 2013). ISARIC4C Investigators are listed in the footnote to this article (ISRCTN66726260; doi:10.1186/ISRCTN66726260). Samples for plasma (2 mL) and tear test strips (TTS) using Schirmer's test (Appendix S1), were collected 1 h pre-dose (C_{min}) and 1 h post-dose (C_{max}). They were collected on Day 5 of tecovirimat treatment and Day 8 of hospital admission. Concomitant medications at the time of sampling are described in Appendix S2.

Tecovirimat concentrations in plasma and tears were determined using validated LC coupled with tandem MS (Appendix S3). The lower limit of quantification for the plasma assay was 5 ng/mL, and for the tear assay was 0.088 ng/mL. The mean plasma tecovirimat concentrations were 18.80 ng/mL pre-dose and 42.34 ng/mL post-dose. Paired TTS concentrations sampled post-dose were from the left eye 292.00 ng/mL and from the right eye 287.50 ng/mL. There were no secondary peaks to suggest degradation. On the day the samples were collected, the serum albumin was 17 g/L.

The C_{min} and C_{max} in plasma were both significantly lower than expected, with C_{min} and C_{max} concentrations previously reported to be 845 ng/mL and 2159 ng/mL respectively.[5] The post-dose concentration of 42.34 ng/mL was taken at 1 h, with no repeated samples. The low level likely reflects that C_{max} was not achieved, which appears to be at 3 h.[6] It appears to be comparable to levels at the same timepoint seen in a previous tecovirimat PK study.[6] Our study also supports previous studies reporting that exposures of tecovirimat are lower in mpox patients when compared with healthy volunteers.[6] Delayed absorption observed in mpox patients as well as nasogastric administration plus critical illness (reduced albumin) and diarrhoea are the likely causes of reduced plasma levels. The patient was also haemofiltered using CVVHF, which may have contributed to the decreased plasma levels, although according to the manufacturer, dose alteration is not needed in haemofiltration and end-stage renal disease.[5]

Both TTS pre-dose and post-dose concentrations exceeded the plasma levels, and post-dose concentrations of plasma and both eyes' tears were over the *in vitro* calculated 90% inhibitory concentration of 37.6 ng/mL.[6] However, it is unclear if there is corneal penetration of tecovirimat, as it took 32 days from restarting the second course of tecovirimat to becoming PCR negative. We did not resample during the ocular disease phase due to the patient's wishes. The authors further suggest more research into the PK/PD of tecovirimat and corneal penetration of tecovirimat.

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Supplementary data

Table S1 and Appendices S1–S3 are available as Supplementary data at *JAC* Online.

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