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1 **Doravirine exposure decreased by dialysis in a HIV patient: a grand round.**

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26

27 **Abstract**

28 Aim: We report the case of a 66-year-old male patient, hemodialysed 3 times per week for
29 chronic renal failure, and treated with 100 mg doravirine once daily in combination with
30 dolutegravir for HIV1. No dose adjustment is required for doravirine in the case of severe
31 renal injury but the effect of dialysis on its exposure is poorly known.

32 Results: Two series of 2 samples were drawn before and after 4-hour-hemodialysis and
33 showed an average decrease of $48.1 \pm 6.7\%$. The effects of hemodialysis were important,
34 contrary to what was expected and previously reported. Additionally, the intra-individual
35 variability was low. Nevertheless, as the concentrations reported were largely above the
36 inhibitory concentration 50 (IC50), no dose adjustment was required.

37 Conclusion: The decrease of doravirin concentration by hemodialysis observed in this case
38 report was quite significant. Therefore, therapeutic drug monitoring might be recommended in
39 some cases for hemodialysed patients treated with doravirin.

40 **Keywords:** doravirine; HIV; haemodialysis; therapeutic drug monitoring; case report

41 Introduction

42 Doravirine is a nonnucleoside reverse transcriptase inhibitor (NNRTI) indicated in the
43 treatment of human immunodeficiency virus 1 (HIV-1) infections. According to the latest
44 European AIDS clinical society (EACS) recommendations
45 (<https://www.eacsociety.org/guidelines/eacs-guidelines/>), anti-retroviral treatment (ART)
46 strategies including NNRTI are adapted to naïve adult patients with HIV. Classical
47 combinations use 2 NRTI + 1 INTI, 2 NRTI + 1 INST or 1 NRTI + 1 INST, and finally 2
48 NRTI + 1 NNRTI. These strategies are facilitated by combination regimens, which provide a
49 combination of the essential characteristics to ensure optimal treatment, such as long-term
50 efficacy, resistance barrier, safety, tolerability and a limited number of drug interactions.

51 Case report

52 Clinician

53 We have a question about a 66-year-old man treated for 12 months with doravirine 100 mg
54 once daily (OD) in combination with dolutegravir 50 mg OD for a HIV1 infection contracted
55 after a blood transfusion and diagnosed in 1984. His ART drug history consists of 12 different
56 drug associations; the changes are mainly due to tolerance issues or just for simplification.
57 The patient has been successively treated with 13 different molecules (nelfinavir, tenofovir,
58 efavirenz, abacavir, saquinavir, emtricitabine, atazanavir, raltegravir, etravirine, rilpivirine,
59 lamuvidine and finally dolutegravir and doravirine). The patient's most recent viral
60 genotyping was performed in 2017 and revealed mutations to the M36I, R41K, and I62V
61 class of protease inhibitors. His viral load has been undetectable (<30 copies/mL, log<1.47)
62 since 2016.

63 The patient's medical history includes post-transfusion hepatitis C complicated by cirrhosis
64 and hepatocellular carcinoma leading to a liver transplant in 2005 which is still functioning.
65 The patient also suffers from haemophilia A, hypertension, atrial fibrillation, severe ischemic
66 heart disease, and insulin-dependent diabetes. Finally, he is on haemodialysis three times a
67 week due to severe chronic renal insufficiency related to an immunoglobulin-A linked
68 nephropathy and a chronic treatment by ciclosporin (glomerular filtration rate estimated with
69 the CKD-EPI formula (eGFR), 7 mL/min). The dialysis characteristics are as follows: 4-hour
70 haemodialysis (bicarbonates) using a Theradial[®] FDX 210 GW dialyser (PEPA[®] membrane)
71 with a blood flow of 400 mL/min. The co-treatments are tacrolimus (1.5 mg OD),
72 hydrocortisone (10 mg OD), sucro-ferric oxide (500 mg OD), lansoprazole (30 mg OD),
73 spironolactone (25 mg OD), warfarin (4 mg OD), insulin aspartate and human insulin.

74 What are the consequences of haemodialysis on doravirine concentrations?

75 **TDM specialist**

76 The effect of renal impairment on doravirine exposure has recently been studied. No
77 significant clinical difference has been observed on doravirine concentrations measured 24h
78 after drug intake (C_{24h}), in patients with an eGFR <30 ml/min/1.73 m² in comparison with
79 controls with eGFR ≥ 80 ml/min/1.73 m² (geometric mean ratio [90% confidence interval] of
80 $C_{24h}=1.38$ [0.99, 1.92]).¹⁻³ The Summary of Product Characteristics (SPC) of doravirine³
81 reports that the effect of dialysis has not been studied. Recently, Molto et al⁴ reported cases of
82 hemodialysis in 8 patients treated with doravirine. They did not recommend dose adjustments
83 because the observed ratio between doravirine concentrations before and after hemodialysis
84 was 0.80. The effect of hemodialysis on dolutegravir concentrations is already known and is
85 not expected to be significant (median extraction ratio of 7%)⁵.

86 We recommend drawing one sample before and one after dialysis to collect information on
87 doravirine extraction. There is nothing in the literature about a possible redistribution of
88 doravirine, as observed for vancomycin just after dialysis⁶. Anyway, we cannot keep an
89 outpatient waiting at the hospital to draw a sample 2h after the end of the dialysis.

90 **Clinician**

91 Two series of 2 samples (before and after dialysis) were collected: in February and March
92 2021, just before and 10 minutes after dialysis in the first case and just before but only 5
93 minutes after for the second (Figure 1).

94 **TDM specialist**

95 The 2 series provide some new information about the intra-individual variability of the effect
96 of hemodialysis on doravirine concentrations, which is currently not known. Doravirine
97 plasma concentrations were measured using a validated LC-MS/MS method which has not
98 been published but has been adapted from Jung et al⁷ by implementation of the LC-MS/MS
99 transitions for the new antiretrovirals). The concentrations measured were respectively 3453
100 $\mu\text{g/L}$ and 1628 $\mu\text{g/L}$ in the first series, leading to a dialysis extraction ratio of 0.47, and 2698
101 $\mu\text{g/L}$ and 1527 $\mu\text{g/L}$ in the second series, leading to a dialysis extraction ratio of 0.57 (Figure
102 1). The reported trough (C_0) and maximum doravirine concentrations (C_{max}) for a dose
103 regimen of 100 mg QD are approximately 396 ± 250 $\mu\text{g/L}$ and 962 ± 183 $\mu\text{g/L}$ ³. The
104 concentrations observed in our patient are much higher than the usual values but they are not

105 C₀ or C_{max}, rendering them rather complicated to interpret. However, with this information,
106 we can estimate the effect of dialysis on doravirin plasma concentrations in our patient.

107 Clinician

108 We question the high concentrations observed in this patient given that doravirine is not
109 eliminated through the kidney (<10% of elimination occurring via the renal pathway¹). It is of
110 note that the results of the fibroscan (performed 2 months before the sample) and liver MRI
111 (performed 10 days before the sample) showed an advanced fibrosis without rejection (grade
112 A1F4) and a dysmorphic cirrhosis liver. Could this explain the high concentrations?

113 TDM specialist

114 The main cause of the high concentrations observed in this patient is probably his cirrhosis.
115 Indeed, the literature^{8,9} and SPC³ recommend caution in patients with severe hepatic
116 impairment, as there are no data on this clinical situation. Another hypothesis could be drug-
117 drug interactions, but no medications known for interacting with doravirine have been
118 identified in our patient's treatment. Notable interactions with doravirine, have only been
119 reported with strong enzymatic inhibitors (ritonavir and ketoconazole), in line with its
120 metabolism by cytochromes CYP450 3A4 and 3A5.^{10,11} However, in the literature, no
121 association has been reported between high concentrations and adverse effects^{11,12}.

122 Clinician

123 We request some advice on the necessity of dose adjustment of doravirine in our patient in the
124 light of the significant decrease of concentrations with dialysis.

125 TDM specialist

126 The average decrease caused by dialysis is $48.1 \pm 6.7\%$ (the standard deviation being small,
127 synonym of a small intra-individual variability). Despite the strong decrease of doravirine
128 concentrations in this patient, there is very little risk that the concentrations become
129 subtherapeutic, given the IC₅₀ of 5.1 µg/L¹³, IC₉₀ of 8.08 g/L in patients with a wild type
130 HIV1 virus or 95% effective concentration with 10% human serum (4.6–12.7 ng/dL
131 according to the NNRTI resistance-associated mutations)¹⁴. The dialysis extraction ratio is
132 slightly different from those reported in the literature⁴ (0.8 vs 0.5 for us). One reason could
133 be, given the large range of concentrations observed by Molto et al, their samples were
134 drawn at different times within the interdose.

135 **Conclusion**

136 Dose adjustment was not recommended in this patient treated by doravirine while on
137 haemodialysis, which is consistent with reports of other patients in similar situations^{4,11,15}.
138 However, the fraction cleared by dialysis in this case report was non negligible. Therefore,
139 therapeutic drug monitoring might be recommended in some cases for hemodialysed patients
140 treated with doravirine especially in those displaying concentrations close to the protein-
141 adjusted IC90.

142 **Declaration of interest:** All authors: none to declare.

143

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198 **Figure legends**

199 Figure 1: Case timeline presenting drug administration, hemodialysis and measurements of
200 drug concentrations.