**Higher than standard meropenem and linezolid dosages needed for appropriate treatment of an intracerebral hemorrhage patient with augmented renal clearance**

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A 57-year-old, 49 kg female was admitted at the Emergency Department after severe intracerebral hemorrhage. Head CT-scan revealed rupture of a saccular aneurysm of the right middle cerebral artery. External ventricular drain (EVD) was placed in the right lateral ventricle to treat hydrocephalus, and endovascular coiling of the cerebral aneurysm was performed.

On day 3, an EVD-related infection was suspected [C-reactive protein (C-RP) of 82.56 mg/L, normal range 0–5 mg/L; and pro-calcitonin (PCT) of 0.87 ng/mL, normal range < 0.10 ng/mL], and empirical antimicrobial therapy was started intravenously with cefotaxime 2 g q8h. On day 8, C-RP was 110.03 mg/L, and antimicrobial therapy was escalated to meropenem [500 mg q6h over 6 h (i.e., by continuous infusion, CI) after 2 g loading] plus linezolid (600 mg q12h intravenously).

Despite escalated therapy, C-RP increased furtherly and peaked on day 13 (241.47 mg/L). Therapeutic drug monitoring (TDM) was performed for assessing drug exposure [desired trough linezolid concentrations (Cmin) of 2–8 mg/L [[1](https://link.springer.com/article/10.1007/s00228-018-2465-x#CR1)] and steady-state meropenem concentrations (Css) of 8–16 mg/L [[2](https://link.springer.com/article/10.1007/s00228-018-2465-x%22%20%5Cl%20%22CR2%22%20%5Co%20%22View%20reference)]. Drug concentrations were measured by means of HPLC assays with UV detection [[1](https://link.springer.com/article/10.1007/s00228-018-2465-x%22%20%5Cl%20%22CR1%22%20%5Co%20%22View%20reference), [2](https://link.springer.com/article/10.1007/s00228-018-2465-x%22%20%5Cl%20%22CR2%22%20%5Co%20%22View%20reference)].

TDM revealed suboptimal exposure for both antibiotics (linezolid Cmin of 0.3 mg/L; meropenem Css of 3.82 mg/L). Suspecting augmented renal clearance (ARC), creatinine clearance (CLCR) was measured on day 16 and 18. Supraphysiological CLCR values confirmed ARC in both occasions (131.0 and 160.2 mL/min, respectively).

Attainment of the desired antibiotic targets was achieved only after three subsequent dosage increases, up to 600 mg q8h for linezolid and to 1500 mg q6h by CI for meropenem.

Afterwards, significant clinical improvement was observed with a consistent drop of both C-RP (24.27 mg/L) and PCT (0.13 ng/mL). Antimicrobial therapy was finally stopped on day 21.

Considering that ARC may lead to augmented drug clearance (CL) [[3](https://link.springer.com/article/10.1007/s00228-018-2465-x#CR3)], we assessed meropenem and linezolid CL. Non-compartmental pharmacokinetic analysis showed that meropenem CL was two to fivefold higher than observed previously in other patient populations (Table [1](https://link.springer.com/article/10.1007/s00228-018-2465-x#Tab1)). Likewise, one-compartment pharmacokinetic analysis of linezolid with Pmetrics [[7](https://link.springer.com/article/10.1007/s00228-018-2465-x#CR7)] showed 1.6-fold higher CL than observed in healthy volunteers (Table [1](https://link.springer.com/article/10.1007/s00228-018-2465-x#Tab1)).

To the best of our knowledge, this is the first report of augmented CL and suboptimal exposure to meropenem and linezolid showed in a cerebral hemorrhage patient with ARC. Noteworthy, ARC may be a very common condition either among patients with non-traumatic subarachnoid hemorrhage [[8](https://link.springer.com/article/10.1007/s00228-018-2465-x%22%20%5Cl%20%22CR8%22%20%5Co%20%22View%20reference)] or in those with traumatic-brain injuries [[9](https://link.springer.com/article/10.1007/s00228-018-2465-x%22%20%5Cl%20%22CR9%22%20%5Co%20%22View%20reference)]. ARC may be the consequence of an increased cardiac output with increased renal blood flow promoted by the vasoactive drugs that are used for attenuating cerebral vasospasm [[8](https://link.springer.com/article/10.1007/s00228-018-2465-x%22%20%5Cl%20%22CR8%22%20%5Co%20%22View%20reference)].

Some studies showed that ARC may be a predictor of suboptimal exposure to beta-lactams in various patient populations [[3](https://link.springer.com/article/10.1007/s00228-018-2465-x%22%20%5Cl%20%22CR3%22%20%5Co%20%22View%20reference)]. Our findings suggest that underexposure to meropenem may occur even in cerebral hemorrhage patients experiencing ARC, and that dosage increases up to threefold might be needed for optimizing drug exposure (i.e., Cmin > 4xMIC) in these cases. Beyond dosage increase, it should be mentioned that in patients with ARC, administration of meropenem by CI (after loading), rather than by intermittent infusion, may furtherly increase the probability of optimal target attainment under the same daily dose [[6](https://link.springer.com/article/10.1007/s00228-018-2465-x#CR6)].

Even linezolid CL was increased in our patient (11.2 vs. 7.4 L/h in healthy volunteers) [[4](https://link.springer.com/article/10.1007/s00228-018-2465-x#CR4)]. This is consistent with the findings of a previous study showing augmentation of linezolid CL (> 9.0 L/h) in 3 out of 5 cerebral hemorrhage post-surgical patients treated for stroke-associated pneumonia [[10](https://link.springer.com/article/10.1007/s00228-018-2465-x#CR10)].

Overall, drug CL increase was much higher for meropenem (2–5 fold) than for linezolid (1.6-fold). This is in line with the renal route having approximately double importance in the elimination of meropenem compared to that of linezolid (60 vs. 30%, respectively).

In conclusion, our findings showed that intracerebral hemorrhage patients with ARC might be at risk of suboptimal exposure during treatment with meropenem and linezolid at standard dosages. Real-time TDM might represent a helpful tool for optimizing antibiotic therapy in these cases.

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| **Table 1.** Mean linezolid and meropenem clearance in the described patient compared to previously reported data |
| Pharmacokinetic parameter | Linezolid |  | 24h-CI meropenem\* |
|  | Patient reported | Healthy subjects [4] |  | Patient reported | Surgical ICU patients [5] | Medical patients [6]  |
| CL (L/h) | 11.2 | 7.4 |  | 21.8 | 10.8 | 4.43 |
| \*Data during CI are lacking in healthy subjects |