Relevance of the drug-drug interactions between lidocaine and the pharmacokinetic enhancers ritonavir and cobicistat

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Published in:
Aids

DOI:
10.1097/QAD.0000000000002162

Publication date:
2019

capillary action until immobilized by anti-Cryptococcal antibodies at the test line, thereby resulting a visible positive test [9].

LFA is also useful for quantification of CrAg by titration apart from the diagnostic (qualitative) purpose, which is clinically important to predict the risk of death and immune reconstitution syndrome [10,11]. LFA employs different dilution steps for qualitative (1 : 2) versus semi-quantitative titration (1 : 5, 1 : 10, 1 : 20, 1 : 40, 1 : 80, 1 : 160 and so on).

In conclusion, when there is high suspicion of cryptococcal meningitis in the setting of a negative CSF CrAg LFA, a serial dilution (i.e. semi-quantitative titration) must be performed to rule out a false-negative test due to the postzone phenomenon.

Acknowledgements

Conflicts of interest

There are no conflicts of interest.

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Received: 25 December 2018; accepted: 3 January 2019.

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DOI:10.1097/QAD.0000000000002157

OPEN

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With great interest we read the article by Antonio *et al*. [1] reporting on the serological response to syphilis treatment with penicillin benzathine or doxycycline in patients with HIV following a manufacturing shortfall of penicillin benzathine. No differences in serological response were observed between the two treatment strategies. Long-acting penicillin formulations, however, remain first-line treatment for syphilis [2]. Dependent on the stage of the infection, treatment is recommended by a single injection of 2.4 million units benzylpenicillin benzathine [early infection (acquired within the last 12 months)] or by three successive weekly injections of 2.4 million units (late infection). Administration of benzylpenicillin benzathine is recommended to be split over two doses of 1.2 million units, each in one buttock [3]. Discomfort of these injections can be reduced by replacing part of the solvent by a lidocaine (lignocaine) solution [3]. In addition to manufacturing shortfalls, treatment with benzylpenicillin benzathine may be complicated by drug–drug interactions between lidocaine and components of HIV treatment regimens, especially with inhibitors of lidocaine metabolism.

Lidocaine is metabolized in the liver by cytochrome P450 3A4 (CYP3A4) to its metabolite monoethylglyxinexylidide

Table 1. Patient characteristics (concomitant), medication and lidocaine serum concentrations.

Patient number	Age (years)	Weight (kg)	cART	Other medication	*T* (min)	Peak (lidocaine) (mg/l)
1	52	90.7	Ritonavir 100 mg qd Emtricitabine 200 mg bid Tenofovir 245 mg bid Darunavir 800 mg qd	Beclomethasone nasal spray 50 μg qd	31	0.2
2	53	93.5	Cobicistat 150 mg qd Elvitegravir 150 mg qd Emtricitabine 200 mg qd Tenofoviralafenamide 10 mg qd	Acenocoumarol on basis of INR Calcium carbonate 1.25 g qd Cholecalciferol 800 IU qd	56	0.5
3	59	78	Ritonavir 100 mg bid Darunavir 600 mg bid Emtricitabine 200 mg qd Tenofovir 245 mg qd Etravirine 200 mg bid	None reported	32	0.6

cART, combination antiretroviral therapy; INR, international normalized ratio; IU, international units; *T*, time after administration.

(MEGX) [4]. To enhance exposure to antiretroviral drugs, such as atazanavir, darunavir and elvitegravir, ritonavir and cobicistat are used as boosters in combined antiretroviral therapy. Ritonavir and cobicistat inhibit CYP3A4, resulting in an increased exposure (increased area under the curve), increased maximum concentration (C_{max}) and increased half-life ($t_{1/2}$) of antiretroviral drugs that are substrates of CYP3A4 [5]. Drug–drug interactions between ritonavir or cobicistat and lidocaine have been suggested to increase lidocaine exposure by more than three-fold [6], complicating treatment with benzylpenicillin benzathine as this interaction may lead to higher plasma lidocaine levels and adverse effects, including neurological and cardiac side effects. Neurological side effects may consist of respiratory depression, convulsion and coma. Cardiac effects may include elevated blood pressure, increased heart rate (HR) and cardiac output with mild intoxications and, with severe intoxications, reduced HR, conduction velocity and contraction of the heart with dilated vessels [7]. The clinical relevance of the interaction between ritonavir and cobicistat and lidocaine during the treatment of syphilis in HIV patients has not been reported thus far.

To determine the relevance of this interaction, lidocaine peak serum levels were determined in three male HIV-positive patients suspect for syphilis infection (refer to Table 1 for details on the patients). Patients were treated with two injections of 1.2 million units benzylpenicillin benzathine dissolved in 2 ml of water for injection and 2 ml of lidocaine 20 mg/ml, according to local guidelines. In total 80 mg of lidocaine was administered by intramuscular injection. Peak concentrations for lidocaine are expected about 30–60 min after intramuscular administration [8]. Lidocaine serum levels were determined with a validated liquid chromatography–tandem mass spectrometry method. Lidocaine peak serum levels were found to range from 0.2 to 0.6 mg/l (Table 1). Therapeutic lidocaine levels for the treatment of arrhythmia are in the range 1.5–6 mg/l [8–10]. Our observations show that the interaction between lidocaine and ritonavir or cobicistat is not of clinical relevance for this specific patient group and lidocaine may be used safely in the treatment of syphilis with benzylpenicillin benzathine. However, if higher doses of lidocaine are administrated, this interaction may become relevant, especially as pharmacokinetic modelling indicates that inhibition of CYP3A4 may result in an increased half-life. In these cases, use of lidocaine should be avoided or lidocaine drug concentrations should be monitored, especially in old patients or patients treated with drugs known to affect hepatic blood flow or metabolism [10].

Acknowledgements

The study was not financially supported by external funding sources.

Transparency declarations: W.F.W.B. reports reimbursement paid to institution for investigator-initiated study from Janssen-Cilag, financial compensation paid to institution for multicenter study by GSK and catering of a symposium by Janssen-Cilag, all outside the submitted work.

Conflicts of interest

There are no conflicts of interest.

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Received: 14 January 2019; accepted: 19 January 2019.

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DOI:10.1097/QAD.0000000000002162

Correspondence: behavioural changes following HIV seroconversion during the historical expansion of HIV treatment in the United States

We read with great interest the article published by Zhu *et al*. [1]. The authors have addressed an important question regarding sexual behaviour in the context of advances in HIV treatment. In their article, the authors report that prior to the availability of HAART, the odds of subsequent engagement in sex with at least two partners, among MSM, decreased after seroconversion. Seroconversion after the widespread availability of HAART was associated with further reduced odds in engaging in these sexual behaviours. These findings challenge the current discussions regarding the association between HIV treatment advances and sexual behaviour. The study drew on data from 4616 MSM collected between 1984 and 2008, comparing men who seroconverted prior to the availability of HAART and after. Given the design of their study, it is still unclear whether the findings are associated with availability of antiretroviral therapy or the temporal trends in sexual behaviour in the United States over this time period [2].

In 2012, the Food and Drug Administration (FDA) approved emtricitabine/tenofovir for reducing the risk of HIV transmission through sexual activity. Since then, discussions have emerged regarding whether widespread use of emtricitabine/tenofovir as preexposure prophylaxis (PrEP) contributes to riskier sexual behaviour among populations already at a high risk of acquiring HIV, a concept termed 'risk compensation' [3]. On the basis of this concept, people taking PrEP or HIV treatment would perceive a reduced risk of acquiring or transmitting HIV and thus will engage in riskier sexual behaviour; however, the authors have shown that for HIV treatment, this reasoning is not applicable in the cohort studied.

Qualitative research exploring the complexities of risk-taking has begun to describe the diverse ways in which PrEP influences sexual-wellbeing from the perspective of MSM [4]. From the limited research that exists, the perceived impacts of PrEP on sexual behaviour vary and may in fact fluctuate over the course of one's life. Hence, it would be valuable to re-examine the cohort described by Zhu *et al*. [1] for changes in sexual behaviour in the current context of treatment as prevention [5] and PrEP availability. Although limitations of the study constrain the conclusions that can be drawn to MSM, if the authors have access to data from the cohort after 2012, it would be worthwhile to examine and comment on whether sexual behaviours among this cohort have changed since the availability of PrEP. Furthering our understanding of how treatment as prevention and PrEP alter sexual behaviour could aid in directing HIV policy and future research.

Acknowledgements

Conflicts of interest

There are no conflicts of interest.

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