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Reference:

Gys Celine, Mortelé Olivier, van Rafelghem Babette, Berry Eleanor, van Nuijs Alexander, Lambert Willy, Jacobs Werner, Schouwers Sofie, Meskal Anissa, Van Hemeldonck Ellen,- Overdose of the HIV medicine Genvoya® in two auto-intoxications
Journal of analytical toxicology / Society of Forensic Toxicologists [Mesa, Ariz.] - ISSN 1945-2403 - 47:1(2023), p. e1-e5
Full text (Publisher's DOI): <https://doi.org/10.1093/JAT/BKAC056>
To cite this reference: <https://hdl.handle.net/10067/1898970151162165141>

Overdose of the HIV medicine Genvoya® in two auto-intoxications

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Abstract

Toxicological data on overdose with HIV-inhibitors is scarce. We present a case report of two independent suicide attempts by self-administered overdose with the same antiretroviral medicine Genvoya® (emtricitabine/elvitegravir/tenofovir alafenamide/cobicistat). Both patients were admitted to the hospital and presented with a loss of consciousness, lactic acidosis, elevated hepatic transaminase levels and hemodynamic instability. While one patient survived with advanced supportive measures, the other passed away. Emtricitabine levels were measured *in vivo* in various consecutive serum samples and post-mortem urine, peripheral and cardiac serum samples and confirmed excessive use in both cases. This is the first time emtricitabine levels following overdose are reported. Although measured concentrations for emtricitabine were quite similar in these cases, metabolic acidosis was more pronounced in the fatal case. The difference in outcome between the two could be due to a difference in physiological status, susceptibility to accumulation and adverse effects, and perhaps a varying interval between ingestion and the start of supportive measures.

Keywords: HIV, suicide attempt, emtricitabine, overdose, AIDS

Introduction

Highly active antiretroviral therapy (HAART) is used in Human Immunodeficiency Virus (HIV) seropositive patients to suppress HIV replication, thereby restoring immune function, reducing morbidity and limiting the risk of transmission (1, 2). The combination treatment with emtricitabine, elvitegravir, tenofovir alafenamide, and cobicistat (F/E/TAF/C) consists of two reverse transcriptase inhibitors (RTI; F and TAF), an integrase strand transfer inhibitor (INSTI; E) and a pharmacokinetic enhancer (C) (3). Toxicological information on overdose with HIV-inhibitors is scarce (4, 5), and reports including analytical measurements of all or some of these compounds are, to our best knowledge, inexistent. We present here a case report of two independent suicide attempts by self-administered overdose with the same HIV-medication.

Case histories

Case 1

Case 1 involves a 40-year-old HIV seropositive male who was staying at a psychiatric care-unit and stated to have voluntarily taken 60 tablets of Genvoya® (containing, respectively, 200 mg F, 150 mg E, 10 mg TAF and 150 mg C per tablet) and 10 g of paracetamol.

Upon transfer to the hospital, the patient collapsed and lost consciousness. In the emergency room, the patient presented with a blood pressure of 50/30 mm Hg and a pulse of 80 beats/min, combined with intense sweating. Upon admission, screening of the urine for drug (ab)use revealed only the use of benzodiazepines and in serum, a paracetamol concentration of 13.8 mg/L (reference values: 10 – 30 mg/L) was measured. The patient was administered 500 mL 0.9% (w/v) NaCl solution, 500 µg phenylephrine and 100 µg noradrenalin to treat the hypotensive crisis, raising the blood pressure to 75/30 mm Hg. Given his hemodynamic instability, the man was admitted to the intensive care unit. HAART and co-medication therapy were discontinued. As the exact time of paracetamol ingestion was unknown, the emergency physicians started N-acetylcysteine antidote therapy.

Blood tests revealed a moderate reversible renal impairment. The estimated glomerular filtration rate by Chronic Kidney Disease Epidemiology Collaboration (eGFR_{CKD-EPI}) decreased from 115 mL/min/1.73 m² on admission to 72 mL/min/1.73 m² within 17 h. However, renal function was restored within 57 h after admission. Arterial blood gas analysis revealed a metabolic acidosis upon admission with a pH of 7.30 (reference values: 7.35-7.45) and bicarbonate concentration of 19.7 mmol/L (reference values: 22.0-26.0 mmol/L).

For nine hours following admission, the lactate concentration increased from 1.68 mmol/L to 3.80 mmol/L (reference value: < 1.80 mmol/L). Furthermore, a rise in hepatic transaminases was observed after admission. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) values, 19- and 17 U/L upon admission, increased to a maximum value of 151 and 264 U/L, after respectively 9 and 17 h. Two days after admission, the patient complained of transient retrosternal chest pain. Based on a negative coronary computed tomography angiography (CTA), observed ST-elevations by electrocardiogram (ECG) and a positive high sensitive troponine I screening (259 ng/L immediately after

presentation of the symptoms, increasing to 819.6 ng/L after 24 h; reference value: < 34.2 ng/L), the occurrence of a type 2 myocardial infarction was diagnosed.

Cobicistat, which is added to the HAART medication as a pharmacokinetic enhancer, is an inhibitor of the metabolising enzyme CYP2D6, a substrate and inhibitor of CYP3A4 and an inhibitor of the P-glycoprotein (P-gp). Drug-drug interactions (DDI) with co-medication of the patient could occur, leading to elevated serum levels of the latter and more pronounced side- and toxic effects (6). Besides Genvoya®, the Case 1 patient was prescribed a number of other pharmaceuticals for his psychiatric illnesses; valproic acid, venlafaxine, quetiapine, trazodone, lorazepam, olanzapine and alprazolam. DDI with the co-medication through CYP3A4 inhibition are reported for quetiapine, alprazolam and venlafaxine (7, 8). However, with exception of alprazolam, only subtherapeutic concentrations of the co-medication were found in the serum sample taken upon admission to the emergency department, possibly indicating poor therapy compliance. Co-medication analyses on this serum sample were performed at a later stage in the context of the case report. The concentrations of the co-medications were measured using validated, routinely applied analytical methods and are included in the Supplementary Information (Section SI-1). HAART was resumed after 7 days; most of the concomitant medications were resumed 4 days after admission, olanzapine after 5 days. The patient was discharged from the hospital after 7 days.

Case 2

Case 2 concerns an 18-year-old male who stated in the early morning to have voluntarily ingested during the night the contents of “the entire packaging” (i.e., 30 tablets) of the same Genvoya® formulation and subsequently collapsed. The medication was likely prescribed to the partner of the patient and the auto-intoxication was probably a consequence of their break-up.

Upon arrival of the emergency services on the scene, the patient had impaired consciousness (Glasgow Coma Scale of 10/15), hypotension (blood pressure 60/30 mm Hg) and a pulse of 90 beats/min. NaCl solution (500 mL of 0.9% (w/v)) was administered twice, restoring the blood pressure to 100/50 mm Hg. Initial laboratory results were as follows: AST 143 U/L, ALT 204 U/L, lactate dehydrogenase (LDH) 337 U/L, creatine kinase (CK) 368 U/L, lactate 2.7 mmol/L, bicarbonate 19.3 mmol/L. The estimated glomerular filtration rate (eGFR_{CKD-EPI}) was 126.6 mL/min/1.73 m². Arterial blood pH was 7.2. Minutes after admission to the emergency room, the patient suddenly developed a junctional heart rhythm of 40 beats/min without functional output and started gasping. Advanced life support with twofold administration of 1 mg adrenalin initially succeeded at restoring spontaneous circulation but episodes of bradycardia, sometimes evolving to pulseless electrical activity, kept occurring. Transthoracic echocardiogram showed hypocontractile left and right ventricles, suggestive of cardiogenic shock. Administration of 3 mg atropine had no result. Rocuronium and etomidate were administered, and the patient was intubated. Laboratory results revealed metabolic acidosis (lactate 6.30 mmol/L, bicarbonate 9.1 mmol/L, arterial blood pH 7.0). The patient was transferred to a tertiary care hospital for extracorporeal

membrane oxygenation (ECMO), but because of long lasting low-flow time, the ECMO-procedure was cancelled. Metabolic acidosis had worsened (lactate 7.6 mmol/L) and hepatic transaminases had risen (AST 803 U/L and ALT 1030 U/L). Treatment was discontinued, and the patient subsequently passed away, approximately 2 h after admission to the emergency room.

Post-mortem histopathology revealed the presence of chronic hepatitis and HIV-related lesions were found in the spleen (i.e. white-pulp depletion, perivascular hyalinisation). However, HIV-infection could not be confirmed because no further medical history was available.

Methods

Samples

Blood samples were taken from the patient in Case 1 upon admission and at 6 other points in time, ranging from 8.3 to 79.3 h after admission. Five mL of whole blood was collected into serum separation tubes by venous blood sampling and transferred to the clinical laboratory of the hospital, where the tubes were centrifuged subsequently before routine analysis (< 30 min). The serum was transferred into tubes without gel and stored at 4 °C. Emtricitabine and co-medication were quantified after 5 days, respectively in all received samples and in the serum sample taken upon admission.

For the patient in Case 2, three post-mortem samples were analysed: urine and peripheral (femoral) blood which were collected during the external post-mortem examination (3 h post mortem), cardiac blood which was sampled during the autopsy (approximately 50 h post mortem). After the autopsy, samples were transferred to the laboratory, where the relevant tubes were centrifuged and all samples were stored at 4 °C until analysed. Other post-mortem samples (e.g. stomach contents, vitreous humour) were available, but were not analysed for the emtricitabine concentration. No remaining tablets were visible in the stomach contents. In a systematic toxicological analysis of the post-mortem collected blood and urine samples, no other toxicants, prescription or illicit drugs were detected.

Analysis

Levels of emtricitabine were quantified in serum and urine samples using an analytical method adapted from (9). Briefly, 100 µL of 0.1% (v/v) formic acid in methanol and the internal standard clomipramine-*d*3 were added (final concentration 1 mg/L) to 50 µL of sample. After vortex mixing and centrifugation, 100 µL of the supernatant was transferred, evaporated to dryness and reconstituted in 50 µL of 60:40 (v/v) water:methanol with 0.1% formic acid. Extracts were analysed using an Agilent 1290 Infinity UPLC coupled to an Agilent 6460 QQQ (Agilent, USA). Chromatographic separation was carried out on a Synergi Polar C18 column (100 x 2.0 mm; 2.5 µm, Phenomenex, The Netherlands) using gradient elution with a mobile phase composed of ultra-pure water with 0.1 % (v/v) formic acid (A) and methanol with 0.1% (v/v) formic acid (B) at a flow of 0.4 mL/min. The injection volume was 2 µL, compounds were ionised using positive electrospray ionisation and mass

spectrometric detection was performed in multiple reaction monitoring (MRM) mode on specific MRM transitions. Further information on the analytical method can be found in Supplementary Information section SI-2. A linear, non-weighted nine-level calibration curve was set up, ranging from 0.05 to 20 mg/L and showing a coefficient of determination $R^2 > 0.99$ (prepared in triplicate). As a quality control measure, the response area of the internal standard clomipramine-*d3* was monitored in each sample and spiked horse serum and blank urine samples were analysed, in duplicate, at two concentrations (1 mg/L and 10 mg/L). Emtricitabine concentrations were measured in triplicate. Samples showing values above the highest calibration level were reanalysed using a twofold dilution prior to extraction, using horse serum for serum samples and ultrapure water for urine.

Results

The response area of the internal standard showed an RSD (%) of 11% over all samples. The spiked horse serum and urine samples showed an accuracy \pm RSD (%) of 92.1 ± 10.0 % at 1 mg/mL and 90.0 ± 8.0 % at 10 mg/mL. The measured concentrations of emtricitabine in the collected serum and urine samples from both cases are displayed in Table 1. Emtricitabine concentrations were measured in triplicate, showing an RSD (%) ranging from 0.2 to 6.1%. Chromatograms of emtricitabine in the analysed samples from Case 2 are presented in the Supplementary Information (figure SI-1).

The measured emtricitabine concentrations in the serum samples of Case 1 over time (Figure 1) show an increase from 0 h to 8.25 h after admission. Emtricitabine is known to exhibit a T_{max} between 1.1 and 3 h for therapeutic doses (10, 11), but could occur later after overdose, possibly in the 0 – 8 h post admission interval in this case.

In literature, half-lives of 10 h (12) and 4-12 h (13) are mentioned for emtricitabine, based on therapeutic concentrations in pharmacokinetic studies. We calculated the half-life of emtricitabine based on the experimental data available from Case 1, using the PKSolver software (14). Using a non-compartmental model, the half-life was calculated to be 20 h in this patient.

Data on urinary levels of emtricitabine following overdose is missing. Given the concentration detected in the urine in Case 2 and the reported half-life of ± 10 h, the time elapsed between the ingestion of the medication and the admission to the hospital (and subsequent decease) cannot be precisely determined.

Discussion

The emtricitabine concentrations measured in the serum samples from both cases confirmed excessive use. Therapeutic concentrations in serum range from <0.1 to 3.0 mg/L after ingestion of 200-600 mg (13, 15). This is the first time emtricitabine levels following overdose are reported.

Reports on post-mortem serum concentrations of emtricitabine are lacking. Given the higher emtricitabine concentration measured in cardiac serum in Case 2 compared to the

peripheral serum and the large apparent distribution volume of emtricitabine (16), it is likely that post-mortem redistribution occurred to some extent, leading to an artificially increased concentration in the cardiac serum (17). As this is the first report of post-mortem emtricitabine concentrations, more data is needed to confirm this finding. Post-mortem collected blood samples are often haemolysed, thus influencing the concentrations of chemicals that are accumulated in red blood cells. As emtricitabine does not exert this behaviour and shows a whole blood/plasma ratio (b/p) of 1.0, it seems unlikely that haemolysis in the post-mortem samples has impacted the measured concentrations (13, 18). All serum samples available in this study were collected in containers with a separating gel, to which certain drugs might adsorb and thus present with an artificially lower concentration in the serum (19-21). It is unknown at this moment whether emtricitabine is susceptible to such adsorption.

In Case 1, the half-life of emtricitabine was calculated to be 20 h, which is longer than described for therapeutic doses in literature. The prolonged experimental half-life might be explained by (a combination of) different factors, of course subject to individual variability. Metabolising enzymes in the liver might be saturated because of overdosing Genvoya®, and as emtricitabine is excreted largely through the urine, (temporarily) reduced renal function as a consequence of the intoxication might also prolong the half-life. In the same fashion, hepatic function might be reduced due to hepatotoxicity (see also below) (3, 13).

As the T_{max} might occur considerably later after overdose in comparison to therapeutic doses, two possible scenarios could have taken place for case 1: (i) the patient was admitted within 3 h post-ingestion of Genvoya® tablets and the T_{max}, with serum concentrations above 17.6 mg/L, occurred between the 0 – 8 h post-admission interval, or (ii) the T_{max} was delayed considerably, in which case the highest serum concentrations might have occurred between the 8 and 17 h sample collections.

In Case 1, withdrawal of the HAART and fluid therapy were sufficient for recovering renal function. Proximal renal tubulopathy is a well described side effect of tenofovir. TAF, the relatively new tenofovir prodrug present in the ingested formulation in this case report, shows much lower renal toxicity compared to the other prodrug tenofovir disoproxil fumarate (22-24). However, it is possible that nephrotoxicity could occur under specific circumstances where tenofovir could accumulate, e.g. overdose (25). In the only other case report of self-administered Genvoya® overdose (30 tablets), blood tests indicated a temporary progressive renal impairment, which was hypothesised due to acute tubular necrosis (4, 5).

A major adverse effect of RTI is mitochondrial toxicity, potentially resulting in a range of toxic side effects including hepatotoxicity with steatosis as well as lactic metabolic acidosis (3, 26). Both patients in this case report showed increasing lactate concentrations and a lowered arterial blood pH, as well as increased concentrations of hepatic transaminases.

In Case 1, a type 2 myocardial infarction was confirmed by ECG and a positive high sensitive troponine I screening. This condition can be caused by a wide range of conditions, leading to an imbalance between myocardial oxygen supply and demand (27). The patient in Case 2 developed cardiogenic shock with episodes of pulseless electrical cardiac activity, but since no ECG or troponine I screening was carried out, the root cause or underlying mechanism of this observation remained unconfirmed. Based on the available data, it remains unclear if the Genvoya® intoxication is directly linked to the occurrence of type 2 myocardial infarction. This is, to the best of our knowledge, the first time that the occurrence of a type 2 myocardial infarction has been described after Genvoya® overdose.

Although conflicting data have been reported on neuropsychiatric adverse events following therapy with INSTIs (e.g. elvitegravir), suicidal ideation and behaviour are acknowledged as uncommon but potential adverse reactions, particularly in case of a pre-existing history of psychiatric illness (3, 4), which is the case for the patient in Case 1.

The reason for the difference in outcome between the two auto-intoxications remains unconfirmed and data regarding overdosing of Genvoya® is scarce. Despite relatively similar concentrations for emtricitabine found in both cases, the metabolic acidosis was more pronounced for the patient in Case 2. Potential explanations could be the inter-individual variability in physiological status and susceptibility to adverse effects of one or more of the compounds present in the Genvoya® formulation. Given the fact that elvitegravir and cobicistat are both substrates of CYP3A4 and cobicistat is also an inhibitor of this enzyme (3, 7, 8), it is possible that a difference in CYP3A4 activity might contribute to a difference in outcome in specific situations where accumulation might take place, such as overdose. This intrinsic variability might be combined with other factors, e.g. a different interval between ingestion and admission to the hospital. Post-mortem gastric content in Case 2 did not contain any remaining tablets, suggesting that these were all digested. However, information about the time of overdose was missing and could not be retrieved. A short interval between an intoxication with Genvoya® and the start of symptomatic and supportive measures clearly is a relevant parameter for a favourable outcome. In case of Genvoya® overdose, timely general supportive measures are recommended (4, 12, 28) and have been proven sufficient in one of two cases discussed in this report.

Conclusion

Two auto-intoxications with the HIV-inhibiting medication Genvoya® resulted in different outcomes, potentially due to a difference in physiological status, susceptibility to accumulation and adverse effects, and perhaps a varying interval between ingestion and the start of supportive measures. Despite Genvoya® being a formulation containing relatively new and safe pharmaceuticals, it is clear that in case of overdose, toxicity can occur. For the first time, emtricitabine levels following overdose are reported, both in serum and urine, in a living patient and post-mortem.

Data availability statement

The data underlying this article are available in the article and in its online supplementary material.

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Figures and tables

Table 1: Measured levels of emtricitabine in all collected serum and urine samples, ordered by case and time of sample collection.

Case	Concentration emtricitabine (mg/L)	Interval after admission (h)	Sample
1	14.5	0	Serum
	17.6	8.3	Serum
	10.6	17	Serum
	4.0	33.3	Serum
	2.7	41	Serum
	2.0	57.3	Serum
	0.8	79.3	Serum
Time after death (h)			
2	14.4	3	Peripheral serum
	22.7	3	Urine
	21.1	49.2	Cardiac serum

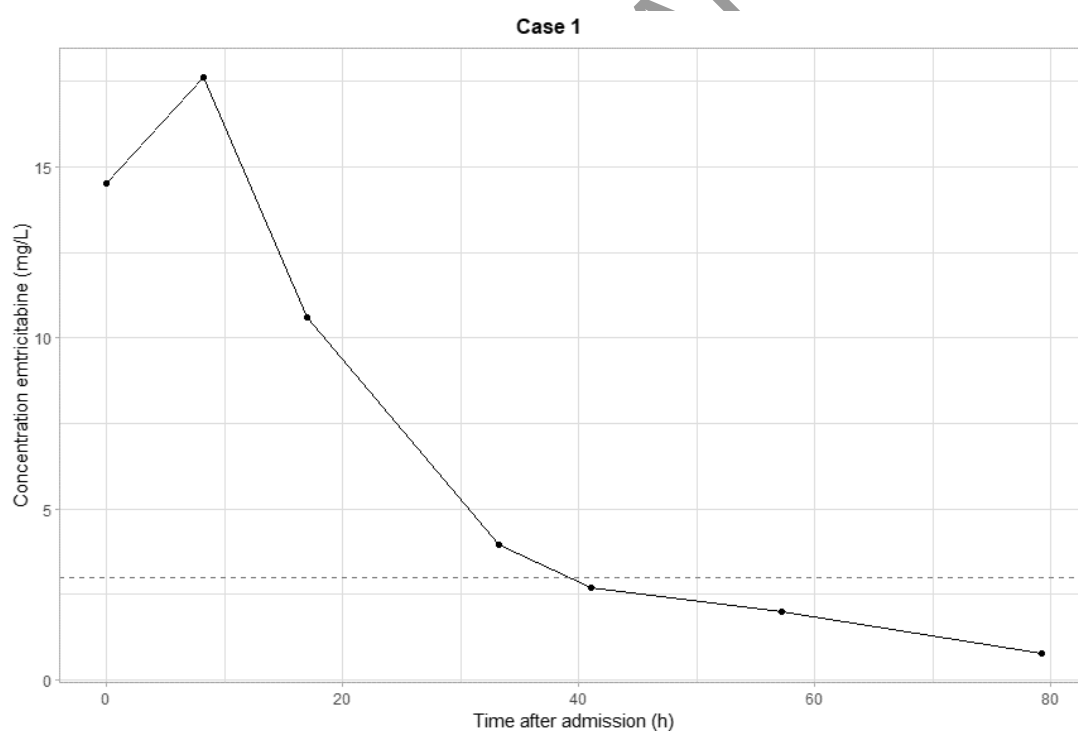


Figure 1: Concentration profile of emtricitabine in serum samples of the patient in Case 1 against the time after admission to the emergency room. The dashed line represents the upper limit of the therapeutic concentration range.