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CASE REPORT

Symptoms, toxicities, and analytical results for a patient after smoking herbs containing the novel synthetic cannabinoid MAM-2201

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Abstract We report a case of intoxication by the synthetic cannabinoid MAM-2201 ([1-(5-fluoropentyl)-1*H*-indol-3-yl] (4-methyl-1-naphthalenyl)-methanone). A 31-year-old man smoked about 300 mg of a herbal blend. He experienced an acute transient psychotic state with agitation, aggression, anxiety, and vomiting associated with a sympathomimetic syndrome. MAM-2201 was detected and quantified in a plasma sample using liquid chromatography-tandem mass spectrometry (LC–MS–MS). The level was 49 ng/ml 1 h after smoking. The use of other drugs was analytically excluded. The presence of MAM-2201 was confirmed in the herbal blend using gas chromatography–mass spectrometry (GC–MS) and LC–high resolution MS. This is the first description of an analytically confirmed intoxication and of the determination of MAM-2201 in human blood plasma.

Keywords Synthetic cannabinoids · MAM-2201 · Symptoms · Toxicological analysis · Spice · LC–MS–MS

Introduction

Cannabis is the most widely produced and consumed illicit substance worldwide [1]. The psychoactive effects of cannabis are mainly due to Δ^9-tetrahydrocannabinol (Δ^9-THC), which acts as a partial agonist on CB_1 and CB_2 cannabinoid receptors [2]. Since the isolation of Δ^9-THC in 1964, hundreds of cannabinoids have been synthesized for biomedical research purposes with the aim of finding new therapeutic agents [2, 3]. More recently, these synthetic cannabinoids have attracted the interest of recreational drug users [4]. Around 2004, herbal and plant mixtures ("spices") emerged as legal alternatives to cannabis in Europe [3]. It was initially assumed that the cannabis-like effects were derived from the plants themselves. However, the suspicion was raised that synthetic compounds added to the herbal blends were the main causes of the pharmacological activities [4, 5]. In 2008, the synthetic cannabinoids JWH-018 and CP47,497 were identified for the first time in "Spice", one of the first commercialized examples of "herbal incense" [6–8]. Since then numerous synthetic cannabinoids have been identified in other herbal and plant mixtures [6, 9–18]. Spice drugs have become popular alternatives to marijuana [19] and an important new class of designer drugs [4, 20, 21].

Here, we present a case of intoxication with the synthetic cannabinoid MAM-2201 ([1-(5-fluoropentyl)-1*H*-indol-3-yl] (4-methyl-1-naphthalenyl)-methanone, CAS 1354631-24-5, Fig. 1) [14, 15, 22], and describe the analytical documentation of MAM-2201 in both herbal blends and blood plasma of the patient. To our knowledge, this is the first described case of an analytically confirmed intoxication with MAM-2201.

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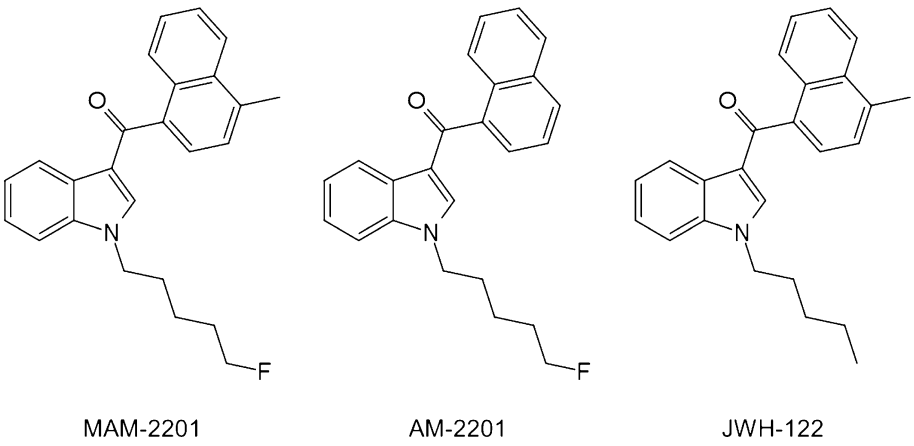

Fig. 1 Chemical structures of MAM-2201 and the related cannabinoids AM-2201 and JWH-122

Case history

A 31-year-old man of Japanese descent smoked a hookah (water pipe) with about 300 mg of "Samurai King", one of two herbal incenses that he had purchased via the Internet (Fig. 2). After a few minutes, he felt increasingly uncomfortable, began to shiver, and vomited several times. Because he became more and more confused and aggressive, his wife alerted the emergency medical services. Thirty minutes after smoking the herbs, paramedics met a highly agitated and confused patient. His pupils were dilated and hardly reacted to light. The Glasgow coma scale score was 13, the pulse rate 144 /min, and blood pressure 160/100 mmHg. The capillary blood glucose was 8.6 mmol/l. During transport to the emergency department, the patient vomited again. At the emergency department, the patient was still agitated and in a state of panic. The patient could not be examined further and had to be isolated. The pulse rate was 120 /min, the blood pressure 136/77 mmHg, respiratory rate 24 /min, and ear body temperature 36.9 °C. Laboratory studies indicated slight hypokalemia at 3.2 mmol/l (normal 3.7–4.7 mmol/l), elevated aspartate alanine transferase at 50 U/l (normal 10–37 U/l), hyperglycemia at 9.5 mmol/l (normal 3.8–6.1 mmol/l), hypocalcemia at 2.06 mmol/l (normal 2.10–2.65 mmol/l), and hypophosphatemia at 0.74 mmol/l (normal 0.80–1.50 mmol/l). The blood count revealed leukocytosis of 13.66×10^9 /l (normal $3.5–10.0 \times 10^9$ /l) with lymphocytosis, monocytosis, eosinophilia, and basophilia, but with a normal neutrophil count. The coagulation parameters were normal. Venous blood gas analysis 1 h after consumption of the product showed respiratory acidosis (pH 7.26, pCO_2 8.04 kPa, pO_2 5.87 kPa, HCO_3 26.4 mmol/l, base excess −1.6 mmol/l, anion gap 10.6 mmol/l) with elevated lactate at 4.5 mmol/l. After 1 h at the emergency department and about 1.5 h after the consumption, the psychological conditions returned to normal. On clinical examination, the pupils were still dilated with slow reaction to light. However, blood pressure (110/50 mmHg) and heart rate (84 /min) had become normal. The electrocardiogram (ECG) 1.75 h after the consumption demonstrated a normal sinus rhythm with a marginally prolonged QTc interval of 440 ms. The patient was discharged 3 h after arrival at the emergency department. An alcohol blood test and a standard drug screening test were negative. Two spice products (Hawaiian 2nd and Samurai King) and a plasma sample of the patient taken approximately 1 h after consumption of the herbal blend Samurai King were used for further toxicological analyses as described below.

Materials and methods

Chemicals and reagents

[1-(5-Fluoropentyl)-1*H*-indol-3-yl](4-methyl-1-naphthalenyl-methanone) (MAM-2201) was obtained from Cayman Chemical (Ann Arbor, MI, USA) and delivered by Adipogen (Liestal, Switzerland). JWH-018-d_{11} was obtained from Chiron (Trondheim, Norway). Water was purified with a Purelab Ultra Millipore filtration unit from Labtech (Wohlen, Switzerland), and acetonitrile of HPLC grade was obtained from Sigma-Aldrich (Buchs, Switzerland). All other chemicals (analytical grade) were from VWR (Dietikon, Switzerland).

Sample preparations for herbal blends

A small amount of each herbal blend (Hawaiian 2nd and Samurai King) was dissolved in 1 ml of methanol and left at room temperature for 10 min. After centrifugation (10,000 *g*, 5 min), the supernatant was transferred to an autosampler vial and analyzed by gas chromatography-mass spectrometry (GC–MS). An aliquot of the extract was diluted tenfold with methanol and analyzed by liquid

Fig. 2 Packaging of the herbal smoking mixtures Hawaiian 2nd and Samurai King

chromatography-high resolution MS (LC–HRMS) as described below.

Plasma sample preparation for general drug screening

Plasma extraction was performed by liquid–liquid extraction (LLE) according to Maurer et al. [23] with slight modifications. Briefly, 200 µl of plasma was extracted with 1000 µl of a mixture of diethyl ether/ethyl acetate (1:1; v/v) after addition of 200 µl of phosphate buffer (500 mM, pH 6). After phase separation by centrifugation, the organic extract was transferred into an autosampler vial. The aqueous residue was then basified with 100 µl of 1 M sodium hydroxide solution and again extracted with 500 µl of the same solvent mixture. The combined organic extracts were evaporated at 50 °C under nitrogen, dissolved in 50 µl of methanol, and analyzed by LC–MS–MS.

Plasma sample preparation for quantification of synthetic cannabinoids

Plasma extraction was performed as described for the above general drug screening with slight modifications. Plasma (50 µl) was first mixed with 10 µl of internal standard (IS, JWH-018-d_{11}, 5 ng/ml), and the procedure that followed was almost the same as described above.

GC–MS conditions

The samples were analyzed using a Thermo Fisher (Zurich, Switzerland) GC–MS system consisting of a Trace GC Ultra, a DSQ II mass selective detector, and an AS 3000 autosampler. The GC conditions were: injection, splitless mode; column, 5 % phenylmethylsiloxane (ZB-5; 30 m × 0.25 mm i.d., 250 nm film thickness); carrier gas, helium; flow rate, 1 ml/min; column temperatures, 80 °C hold for 2 min, increased to 290 °C at 30 °C/min and hold for 15 min. The MS conditions were: ionization, electron ionization (EI) mode; source temperature, 250 °C; solvent delay, 5 min; detection, full scan mode (*m*/*z* 50–600).

LC–HRMS conditions

Analysis was performed using a Dionex UltiMate 3000 UHPLC coupled to an ABSciex 5600 TripleTOF HR mass spectrometer with Analyst software (Version 1.6, AB Sciex, Darmstadt, Germany). The LC settings were: column, Phenomenex (Aschaffenburg, Germany) Synergi Polar-RP (100 × 2.0 mm i.d., particle size 2.5 µm); mobile phase components, 25 mM ammonium acetate buffer in water containing 0.1 % (v/v) acetic acid (A) and acetonitrile containing 0.1 % (v/v) acetic acid (B). The flow rate was 0.5 ml/min with the following gradient program: 0–1 min 5 % B, 1–6 min to 20 % B, 6–10 min to 80 % B, 10–13 min to 90 % B, 13–14 min to 100 % B, hold at 100 % B for 1 min, and at 15.01 min reequilibration to 5 % B for 2 min. The MS ionization conditions were: interface, electrospray ionization (ESI) positive mode; gas 1 and 2, nitrogen (50 psi); ion spray voltage, 4500 V; ion-source temperature, 300 °C; curtain gas, nitrogen (25 psi); declustering potential, 80 V. Time-of-flight (TOF) MS conditions were: scan range, *m*/*z* 100–700; accumulation time, 0.25 s; collision energy, 5 eV. Enhanced product ion (EPI) scan conditions were: scan range, *m*/*z* 100–700; accumulation time, 0.099 s; collision energy spread, 35 ± 15 eV. Information dependent data acquisition (IDA) settings were programmed for the first, second, third, and fourth most intense ions, which exceeded

intensities of 200 cps using dynamic background subtraction. The exclusion time was 10 s. Mass calibration of the TOF instrument was performed by external calibration prior to analysis.

LC–MS–MS conditions

The analysis was performed using a Dionex UltiMate 3000 HPLC system coupled to an ABSciex 5500 Qtrap linear ion trap (LIT) quadrupole mass spectrometer (AB Sciex) with Analyst software (Version 1.5.2). The MS conditions were: ion source, Turbo T operated in positive ESI mode; gas 1, nitrogen (50 psi); gas 2, nitrogen (60 psi); ion spray voltage, 5500 V; ion-source temperature, 450 °C; curtain gas, nitrogen (20 psi), collision gas, medium. For general drug screening, IDA was used after multiple reaction monitoring (MRM) with two transitions per analyte as survey scans. EPI spectra were recorded using the following parameters: scan rate, 10,000 Da/s; scan range, *m/z* 50–550; collision energy spread, 35 ± 15 eV; profile mode. IDA settings were programmed for the MRM transitions that exceeded intensities of 2000 cps. The exclusion time was 4 s. EPI spectra were processed versus an in-house library using Analyst Software 1.5.2.

For quantification of MAM-2201, the same LC–MS–MS conditions were applied as described above, but only MRM transition conditions for MAM-2201 and the IS JWH-018-d_{11} were as follows. For MAM-2201, MRM 1: ion transition, 374.2/169.1; declustering potential (DP), 161 V; collision energy (CE), 37 eV; entrance potential (EP), 10 V; collision exit potential (CXP), 14 V. MRM 2: ion transition, 374.2/115.1; DP, 161 V; CE, 99 eV; EP, 10 V; CXP, 12 V. MRM 3: ion transition, 374.2/232.2; DP, 161 V; CE, 35 eV; EP, 10 V; CXP, 12 V. For the IS JWH-018-d_{11}, MRM 1: ion transition, 353.1/155.1; DP, 111 V; CE, 35 eV; EP, 10 V; CXP, 14 V. MRM 2: ion transition, 353.1/127.1; DP, 111 V; CE, 71 eV; EP, 10 V; CXP, 14 V. MRM 3: ion transition, 353.1/225.1; DP, 111 V; CE, 35 eV; EP, 10 V; CXP, 14 V. Quantification was performed via a five-point calibration curve as described under the method validation.

Method validation for MAM-2201 determination

A simplified method validation was performed as recommended for single case analysis [24] including specificity, matrix effects, limit of quantification, and accuracy and precision studies.

Specificity

Six blank plasma samples from different sources were analyzed for peaks interfering with the detection of MAM-2201 or the IS. Two zero samples (blank sample + IS) were analyzed to check for appropriate IS purity and the presence of native analytes.

Calibration

Calibration was performed in duplicate at the following five concentration levels: 0.05, 0.1, 10, 20, and 50 ng/ml. The regression lines were calculated using weighted (1/X) least-squares regression models to account for unequal variances (heteroscedasticity) across the calibration range. The back-calculated concentrations of all calibration samples were compared to their respective nominal values and quantitative accuracy was required within 20 % of the target.

Accuracy and precision

Six quality control (QC) samples at low (0.2 ng/ml) and high (40 ng/ml) concentrations were analyzed. QC concentrations were determined via the respective calibration curves. Accuracy was calculated in terms of bias as the percent deviation of the calculated mean concentration at each concentration level from the corresponding theoretical concentration. Precision was calculated as relative standard deviation (RSD).

Matrix effects

Matrix effect (ME) studies were performed at QC low and high concentrations using six different plasma sources according to the previous report [25].

Quantification limits

The limit of quantification (LOQ) of the method was defined as a concentration giving the signal-to-noise ratio of 10:1. The lowest point of the calibration curve was set to be the LOQ concentration.

Results and discussion

Symptoms and toxicities

The present case report is the first description in the scientific literature of an analytically confirmed intoxication with the synthetic cannabinoid MAM-2201. MAM-2201 had been first identified as an ingredient of herbal smoking blends in summer 2011 [15, 22]. It is structurally related to the known synthetic cannabinoids AM-2201 and JWH-122 and is therefore also referred to as 4′-methyl-AM-2201, AM 2201-pMe, and 5″-fluoro-JWH-122 (Fig. 1). Due to the structural relationship to AM-2201 and JWH-122, it

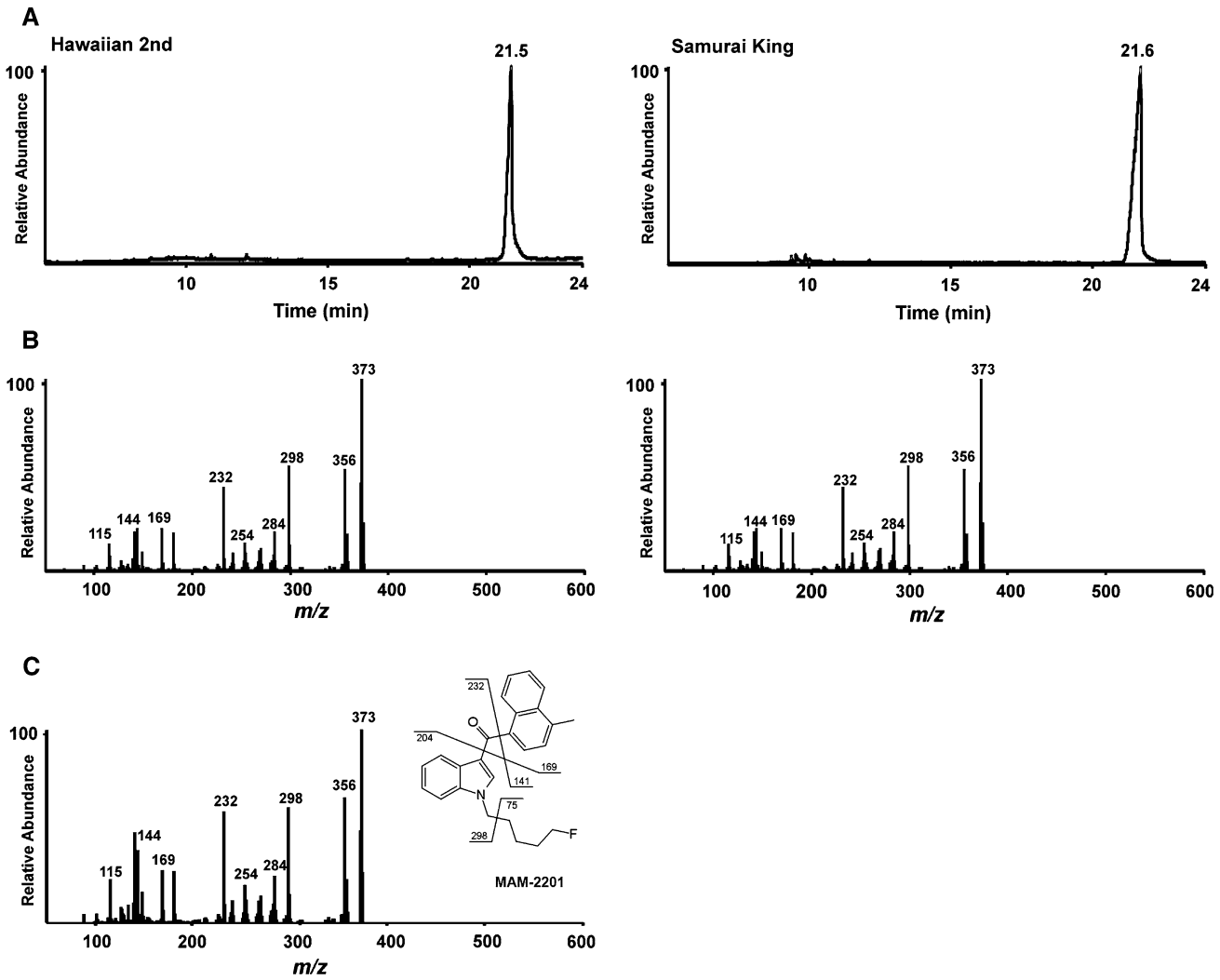

Fig. 3 Total ion chromatograms (**a**) and electron ionization mass spectra (**b**) of Hawaiian 2nd (*left side*), Samurai King (*right side*) and the authentic MAM-2201 (**c**) recorded by gas chromatography–mass spectrometry

can be assumed that MAM-2201 would have similar pharmacological properties to those of the two cannabinoids. In fact, similar effects to those of AM-2201 have been described by recreational users on the Internet (http://www.drugs-forum.com, http://www.bluelight.ru, http://www.eve-rave.ch). Of note, the used and recommended doses for MAM-2201 appear to be smaller than those of other cannabinoids, and it is reported to have longer-lasting effects. MAM-2201 was reported to be active at doses as low as 500 μg and to have a very steep dose–response curve (http://www.wiki.bluelight.ru). Panic attacks and vomiting are noted as typical symptoms at higher doses. However, scientific clinical data on MAM-2201 are lacking.

In our patient, psychotic symptoms and vomiting were the predominant symptoms. Confusion, agitation, aggression, paranoid thinking, and anxiety are common symptoms after consumption of synthetic cannabinoids [4, 20, 26–30]. In addition, we observed sympathomimetic effects including mydriasis and increases in blood pressure and heart rate. Cannabis and synthetic cannabinoids produce tachycardia and hypertension [31–36], and myocardial infarction has been associated with the use of both cannabis and synthetic cannabinoids [37]. Cannabinoids stimulate the sympathetic nervous system to release norepinephrine [34]. Similarly, mydriasis results from central stimulation of the sympathetic efferent pathways by cannabinoids [38]. However, the cardiovascular effects of cannabinoids are complex and also include sympathoinhibition [39].

The effects of the synthetic cannabinoids appear to be short-lived in contrast to those of some designer amphetamine derivatives that may produce sympathomimetic toxicity for up to 72 h or longer [31, 40]. Supportive care

(e.g., monitoring and/or hydration) and a quiet environment seem sufficient to treat most cases of acute intoxication by synthetic cannabinoids. Patients who present symptoms of anxiety, panic, agitation, and arousal may benefit from the use of benzodiazepines [31]. However, special attention is needed for the risk of cardiovascular complications; ECG and cardiac enzymes should be monitored to exclude myocardial ischemia.

The hyperglycemia and increases in white cell blood count in our patient were interpreted as a consequence of stress. In our case, the medical information and the herbal mixtures provided were suggestive of intoxication with any synthetic cannabinoid. Nevertheless, because of the strong sympathomimetic reaction, a mixed-type intoxication could not be excluded initially.

Analysis of herbal blends

As shown in Fig. 3, GC–MS analysis of both herbal blends revealed one major peak per product at 21.5 and 21.6 min for Hawaiian 2nd and Samurai King, respectively. The underlying EI mass spectra were identical in both herbal blends as shown in Fig. 3b. Further analysis by LC–HRMS again revealed identical compounds in both herbal blends with exact protonated molecular ions of *m/z* 374.1916 and 374.1915 for Hawaiian 2nd and Samurai King, respectively. These accurate masses correspond to a molecular formula of $C_{25}H_{25}FNO$. A closer look at the fragment ions gave a hint for typical fragmentation of synthetic cannabinoids of the JWH family [41] with the major fragment at *m/z* 169.0652 indicating a molecular formula of $C_{12}H_9O$ and *m/z* 232.1137 indicating a molecular formula of $C_{14}H_{15}FO$ as exemplified for Samurai King in Fig. 4. In comparison with other already known synthetic cannabinoids, these findings suggested the presence of a methyl group at the naphthyl moiety, similar to that of JWH-122, and a fluorine atom in the pentyl chain as in AM-694. SciFinder search with these suggestions gave the hint for MAM-2201. Final comparison of retention time and mass spectra in GC–MS and LC–HRMS versus commercially available MAM-2201 confirmed its identity for both herbal blends.

Drug screening and MAM-2201 quantification for plasma sample from patient

Screening of the plasma sample by LC–MS–MS revealed only the presence of MAM-2201 and caffeine. No other drugs, such as cocaine, amphetamines, or other synthetic cannabinoids, could be detected in the sample. Unfortunately, no urine was available to perform a broader screening analysis.

Quantification over a five-point calibration curve as described under the method validation revealed an

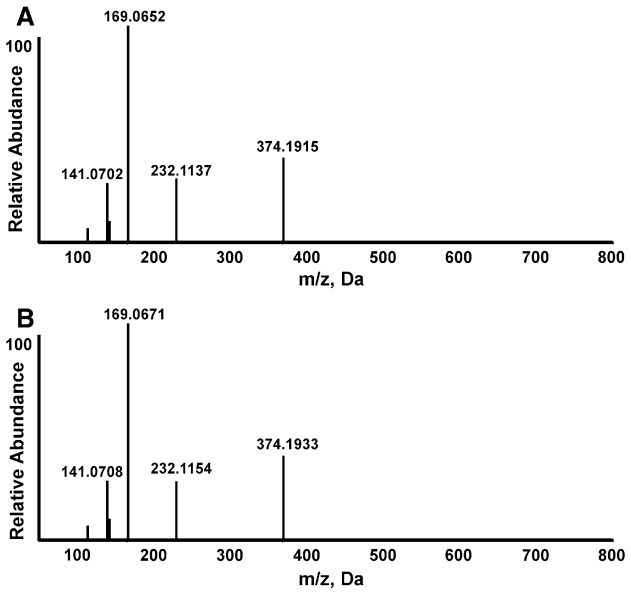

Fig. 4 Enhanced product ion mass spectra obtained from the precursor ion at *m/z* 374 recorded for herbal blends of Samurai King (**a**) and the reference MAM-2201 (**b**) analyzed by liquid chromatography–high resolution mass spectrometry

MAM-2201 concentration of 49 ng/ml in the patient's plasma sample. A simplified method validation was performed with regard to specificity, accuracy, precision, matrix effects, and LOQ. Accuracy was 92.3 % for the low concentration and 97.5 % for the high concentration. Precision data were 9.3 and 7.3 % for the low and high QC samples, respectively. Matrix effects were within the required limits with 107 % (RSD 15.6 %) and 90.0 % (RSD 7.1 %) for low and high concentrations, respectively. The LOQ was consistent with the lowest calibrator concentration with less than 20 % bias. The limit of detection (LOD) was not systematically evaluated.

Conclusions

To our knowledge, this is the first description of the clinical symptoms of MAM-2201 intoxication. Furthermore, this is also the first report of identification and quantification of MAM-2201 in a human plasma sample in an actual intoxication case.

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