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Toxicological analysis and toxicokinetics in an acute fluoxetine and trimipramine intoxication

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BACKGROUND: Selective serotonin reuptake inhibitors (SSRIs, e.g. fluoxetine) have increasingly replaced tricyclic antidepressants (TCAs, e.g. trimipramine) in the treatment of depression. Fluoxetine inhibit reuptake of the neurotransmitter serotonin. Trimipramine is a moderate reuptake inhibitor of norepinephrine and a weak reuptake inhibitor of serotonin and dopamine. Overdose of these two inhibitors causes tachyardia and drowsiness. We present an apparent suicidal attempt in which fluoxetine and trimipramine were the causative agents.

CASE HISTORY: The patient was a 25-year-old woman (african-caucasian) who was diagnosed as suffering from depression (borderline personality disorder), and was prescripted fluoxetine and trimipramine for treatment. In a suicidal attempt she ingested one hundred 20 mg fluoxetine tablets. Approximately five hours later, she came to hospital. She had a bruise at the left eyebrow and experienced several grand mal seizures. For primary detoxification, carbo medicinalis and magnesium sulfuricum were administered. During six consecutive days, serum concentrations of fluoxetine (F), norfluoxetine (NF), trimipramine (T) and nortrimipramine (NT) were measured. The patient left hospital after 6 days without any sequel.

METHODS: Within the scope of systematic toxicological analysis, the first sample was investigated by HPLC-DAD. F, NF, T and NT were identified, but both metabolites elute with poor resolution. A LC-ESI-MS/MS method (Shimadzu, API 3000) we previously developed for the simultaneous identification and quantification of selective antidepressants and neuro-leptics with the TDM was therefore adopted. The method covers nine antidepressants (amitriptyline, clomipramine, doxepine, fluoxetine, imipramine, maprotiline, paroxetine, sertraline, trimipramine) and some of their respective active metabolites (nortriptyline, norclomipramine, nordoxepine, norfluoxetine, desipramine, normaprotiline, norsertraline, nortrimipramine) and two neuroleptics (chlorprotixene and levomepromazine). Trimipramine-D3 (298.0 m/z -> 103.0 m/z) and clomipramine-D3 (318.2 m/z -> 89.0 m/z) were used as internal standards. The LC-MS/MS method is based on a simple precipitation step. Analytical separation was carried out using a Phenomenex Luna 5µ C8 (2) column (2.0 x 30 mm). The gradient consisted of a mixture of solvent A (methanol: 0.1% HAc with 10 mM NH_4Ac 97:3) and solvent B (0.1% HAc with 5 mM NH_4Ac: methanol 90:10). The flow rate was 0.6 mL/min, the oven temperature was 25oC and the time for analysis was 5 min. The compounds were quantified in the multiple reaction monitoring mode with focus on the masses [m/z], (+) ESI: F: 310.1-> 148.1, NF: 296.0->134.0, T: 295.1 -> 99.8, NT: 281.2-> 208.0) using calibration curves. The lower limit of quantification is 5 µg/L (S/N >10).

RESULTS: Our LC-MS/MS method for the simultaneous identification and quantification of selective antidepressants and neuroleptics within the TDM proves to be superior for the intoxication case. For quantification a 6-point calibration (5, 10, 50, 100, 250 and 500 µg/L) was performed. The day-to-day precision CVs (100 and 200 µg/L) ranged from 2.3 to 4.4%. At the time of hospitalization the maximum serum concentration of F was 1890 µg/L. NF concentration reached its maximum (425 µg/L) two days later. Half-live of F was calculated at 60 h. The concentration-time profile of T showed a distinct delayed resorption with a maximum concentration of 278 µg/L. It was impossible to calculate the half-life of detoxification (NT maximum concentration: 429.3 µg/L). From the area under the curve (AUC) and the population pharmacokinetic data the following bioavailable doses were calculated: F: 4520 mg and T: 1640 mg.

CONCLUSION: Quantitation of trimipramine and fluoxetine (including their metabolites) were carried out with a fast and reliable analytical method using LC-ESI-MS/MS. In a case of an acute intoxication with fluoxetine and trimipramine, maximum concentrations of 1890 µg/L (fluoxetine), 425 µg/L (norfluoxetine), 278 µg/L (trimipramine) and 429 µg/L (nortrimipramine) were measured. The patient absorbed approx. 4520 mg fluoxetine and 1640 mg trimipramine. In this case, fluoxetine has half-life of 60 h. The concentration-time profile of trimipramine shows delayed resorption.

KEYWORDS: *Intoxication, Fluoxetine, Trimipramine, Toxicokinetics, LC-MS/MS*

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