The distribution of Doxepin and Sulpiride in a human poisoning death

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Abstract: An unusual case is reported in which death was caused by doxepin and sulpiride toxicity. A 47-year-old woman committed suicide by oral ingestion of excessive doxepin and sulpiride. Histological examination revealed generalized stasis and we observed bronchopneumonia and chronic thyroiditis. Toxicological analyses by liquid-liquid extraction, gas chromatography-mass spectrometry (GC/MS) and LC-ESI-MS/MS analysis were carried out to identify and quantify the individual substances present in postmortem specimens.

Doxepin concentrations were as follows: heart blood 16.3 μg/mL, subclavian vein blood 9.4 μg/mL, bile 15.8 μg/mL, gall bladder 4.4 μg/g, heart 3.9 μg/g, liver 75.9 μg/g, lung 54.6 μg/g, kidney 15.1 μg/g, cerebral 4.4 μg/g, gastric content 38.7 μg/mL and muscle 2.4 μg/g. Sulpiride concentrations were: heart blood 93.3 μg/mL, subclavian vein blood 97.3 μg/mL, bile 454.0 μg/mL, gall bladder 236.0 μg/g, heart 41.1 μg/g, liver 11.0 μg/g, lung 35.5 μg/g, kidney 16.2 μg/g, cerebral 7.5 μg/g, gastric content 53.3 μg/g and muscle 19.3 μg/g.

In this case, doxepin and sulpiride concentrations in heart blood or subclavian vein blood were higher than literature reported lethal blood levels. However, these data demonstrate that doxepin and sulpiride have different distribution throughout the body. Doxepin and sulpiride are rapidly absorbed following oral ingestion and distribute into well-perfused tissues (lung, liver, heart and kidney) and then redistribute into skeletal muscle. Higher concentrations are present in bile, primarily due to hepatic metabolism.

Key Words: Doxepin, Sulpiride, Postmortem distribution

Doxepin (3-dibenz[b,e]oxepin-11(6H)-ylidene-N,N-dimethyl-1-propanamine, Dox) is a psychotropic agent with tricyclic antidepressant and anxiolytic properties, was evaluated clinically as an antidepressive agent as early as 1963 [1-2], and is used to treat depression, anxiety disorders, and as a second line treatment of chronic idiopathic urticaria. Also, among all antidepressive agents, doxepin is frequently involved in suicide and narcotic drug-related deaths [3]. Its oral bioavailability is about 25%, main metabolite is desmethyldoxepin. Doxepin’s half-life is 17 hours, and desmethyldoxepin is 51 hours. Sulpiride is a first generation, or typical antipsychotic drug of the benzamide class used mainly in the treatment of psychosis associated with schizophrenia and major depressive disorder[4]. Sulpiride is more commonly used in China and Europe. The drug has strong chemical and clinical similarities to the related antipsychotic amisulpride. Despite above 40 years the presence of sulpiride on the pharmaceutical market, the acute poisonings are poorly reported in the medical literature [5]. Sulpiride is absorbed slowly from
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the gastrointestinal tract, usually given in 2 or 3 divided doses. Its oral bioavailability is only 25 to 35% with marked interindividual differences. The peak plasma concentration is reached 4.5 hours after oral dosing. The usual half-life is 6 to 8 hours. Ninety-two percent is excreted unchanged in the urine.

Doxepin and sulpiride associated death was not reported in literature. Exposure to combinations of chemicals that act by a common mechanism of action may result in cumulative effects. We therefore determined Dox and sulpiride in body fluids and tissues in a death by a validated gas chromatography-mass spectrometry (GC/MS) and LC-ESI-MS/MS method.

Case history

A 47-year-old woman committed suicide by oral ingestion of doxepin and sulpiride. The external examination revealed no external signs of injury. A complete autopsy was performed 6 days after death, specimens were collected include (heart blood, subclavian vein blood, bile, gall bladder, heart, liver, lung, kidney, cerebrum, gastric content and muscle). All samples were collected and stored at -20°C until analysis. Histological examination revealed generalized stasis and we observed bronchopneumonia and chronic thyroiditis.

Materials and methods

Chemicals and reagents

All chemicals were analytical grade with purity greater than 98% and were supplied by Sigma. Doxepin, sulpiride and SKF525A standards (1 mg/mL in ethanol) were obtained from Institute of Forensic Science Ministry of Public security P.R.C.

Sample preparation and extraction

One milliliter of blood, bile and one gram of the other samples were brought with distillate water to a volume of 3 mL, and then homogenized in a 10 mL tube of centrifuge (3000×g, 10 min). Prior to vortex for mixed, internal standard solution (SKF525A) was added for final concentration of 3 μg/mL. The solution was brought to pH of 10 with the addition of NaOH 2 M. To each sample, 5 ml of ethyl ether was added.

After horizontal agitation during 10 min and centrifugation at 3000 rpm for 5 min, the organic extract was transferred into a glass tube then evaporated to dryness at 40°C under a gentle stream of air. The residues were reconstituted by 50 μL of ethanol, one micro liters were injected into the GC/MS and two micro liters were injected into the LC-ESI-MS/MS.

Instrumentation and MS/MS conditions

The doxepin analyses were performed with a Thermo-Fisher gas chromatography/mass spectrometry system: GC/DSQ. Capillary column DB5-MS 30 m× 0.25 mm × 0.25 mm were used for analysis. Carrier was helium at the flow rate of 1 ml/min. Injector temperature, 280°C, injection mode was split, split ratio, 50:1. Transfer line temperature, 250°C. Ion source temperature, 250°C. The column temperature program used for doxepin was: initial temperature 100°C for 1 min, 20°C/min to 280°C, maintained for 4 min. The instrument was used in full scan EI (70 eV) mode, scanning in the range between 40–650 m/z.

The sulpiride were performed with a Waters ACQUITY UPLC/TQ DETECTOR, ion mode: ES+, capillary voltage 1.70kv, cone voltage 38v, extractor 2v, Rf voltage 0.5 v, desolvation gas flow: 808 L/Hr, cone gas flow: 53 L/Hr, source temp: 120°C, cone temp: 350°C, ion energy: 0.5. The chromatographic separation was achieved on an Waters ACQUITY UPLC BEH C18, 1.7μm, 2.1×50mm column, thermostated at 30°C. Mobile phase A was methanol, B were 0.2% ammonium acetate and 0.1% formic acid (v/v).

Results

GC/MS chromatogram of doxepin (Figure 1) and LC/MS/MS chromatogram of sulpiride (Figure 2) in extracted blood.

Case results

Doxepin concentrations were as follows: heart blood 16.3 μg/mL, subclavian vein blood 9.4 μg/mL, bile 15.8 μg/mL, gall bladder 4.4 μg/g, heart 3.9 μg/g, liver 75.9 μg/g, lung 54.6 μg/g, kidney 15.1 μg/g, cerebrum 4.4 μg/g, gastric content 38.7 μg/mL and muscle 2.4 μg/g. (Fig.3.)

Sulpiride concentrations were: heart blood 93.3 μg/mL, subclavian vein blood 97.3 μg/mL, bile 454.0 μg/mL, gall bladder 236.0 μg/g, heart 41.1 μg/g, liver 11.0 μg/g, lung 35.5 μg/g, kidney 16.2 μg/g, cerebrum 7.3 μg/g, gastric content 53.3 μg/mL and muscle 19.3 μg/g. (Figure 4.)

Discussion

In this case, doxepin and sulpiride concentrations in heart blood or subclavian vein blood were higher than literature reported lethal
blood levels [2, 6-8]. The variability of doxepin and sulpiride’s pharmacokinetics, chemical structure, toxic ranges, the overlap between therapeutic and as well as postmortem redistribution makes interpretation of analytical results difficult. However, these data demonstrate that doxepin and sulpiride have different distribution throughout the body. Doxepin and sulpiride are rapidly absorbed following oral ingestion and distribute into well-perfused tissues (lung, liver, heart and kidney) and then redistribute into skeletal muscle.

Post-mortem redistribution, in which drug concentrations in blood specimens from various areas of the body change during the post-mortem interval, has been observed for many drugs. This is believed to occur largely through diffusion from a high to a low concentration and is believed to be time dependent. The extent to which a drug undergoes post-mortem redistribution is also dependent on protein binding and lipophilicity.
Drugs with high volumes of distribution, i.e. greater than 3 L/kg, are thus more prone to post-mortem redistribution [9–11]. Doxepin’s Vd is 9–33L/kg. Sulpiride’s Vd is 18–30L/kg. Doxepin and sulpiride is also having higher protein binding and lipophilicity. So doxepin and sulpiride have postmortem redistribution phenomenon. Doxepin central blood concentration was approximately 1.7 times that found in peripheral blood and sulpiride was 0.96. It indicated that postmortem redistribution was correlated with dose and the interaction of doxepin and sulpiride. Higher concentrations are present in bile, primarily due to hepatic metabolism.

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References