

Fatal Adverse Reaction to Ketorolac Tromethamine in Asthmatic Patient

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Abstract: A case of an asthmatic woman who collapsed within a few minutes after intramuscular ketorolac tromethamine (KT) injection is reported. Autopsy findings revealed anatomic evidence of a recent asthma attack. KT was found to be present in the blood at a concentration within the therapeutic range and consistent with the administered dose. Based on the timing of the collapse in relation to the KT administration, death was attributed to an adverse reaction to KT, resulting in acute bronchospasm and cardiac arrest, with asthma as an underlying contributing factor. In this case, asthma alone was not responsible for the death of the patient but only a contributing factor. Physicians have to be aware that in asthmatic patients bronchospasm can be induced by drugs among which aspirin or nonsteroidal anti-inflammatory drugs such as KT are the most common; therefore, death may have an iatrogenic cause. The paper also describes the pathogenic mechanism of an adverse reaction to such drugs and analytical methods for the isolation and detection of KT in postmortem blood.

Key Words: ketorolac tromethamine, adverse drug reaction, anaphylaxis, anaphylactoid reaction, asthma

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Ketorolac tromethamine (KT) is a nonopioid analgesic that belongs to the general class of drugs called nonsteroidal anti-inflammatory drugs (NSAIDs). The drug action on the cyclo-oxygenase pathway of arachidonic acid metabolism seems to be the main mechanism for the analgesic and anti-inflammatory activity¹ even if the analgesic effect of KT is greater than the anti-inflammatory effect. KT decreases pain perception by blocking the pain message to the brain and pain relief may occur within a few minutes after drug administration.¹ Analgesic properties are comparable with those of morphine but without central nervous system depressant effects, which makes KT suitable for postoperative pain management.² In fact, KT is commonly used for acute,

short-term relief of pain such as in the treatment of lower back pain, migraines, cancer, postpartum, and dental pain.¹

KT also reduces inflammation and fever respectively through inhibition of prostaglandin synthesis and dilatation of blood vessels so that heat is lost from the body.¹ It is the only NSAID that can be given by injection in a muscle or vein because of the tromethamine salt that enhances the drug's water solubility.¹ Among the side-effects, KT can provoke gastric ulcer perforation,³ acute pancreatitis,⁴ platelet dysfunction resulting in prolonged bleeding, and severe postoperative hemorrhage.⁵ Renal insufficiency associated with intramuscular administration of KT has also been reported.⁶ In general, the adverse events associated with KT are similar to other NSAIDs.

It is well known that NSAIDs are among the most frequent causes of adverse drug reactions and anaphylaxis is the most severe systemic form of immediate hypersensitivity.⁷ In fact, anaphylaxis is a severe allergic reaction that occurs rapidly after re-exposure to an antigen and causes a life-threatening response involving the whole body.⁸ It is a systemic reaction caused by antigen-specific cross-linking of IgE molecules on the surface of tissue mast cells and peripheral blood basophils, which results in the immediate release of potent mediators.⁸ The clinical symptoms sometimes consist of anaphylactic shock, bronchospasm, angioedema, and various skin eruptions but more often they only resemble an allergy (pseudo-allergic reactions). In fact, pseudo-allergic or anaphylactoid reactions are a group of non-IgE-mediated reactions that must be differentiated from immune-mediated syndromes, but they can also be caused by several drugs such as opiates and NSAIDs.^{9–10}

Nonimmune reactions are also immediate and systemic and can mimic anaphylaxis but are not caused by an IgE-mediated immune response.¹⁰ Such reactions, often severe, are caused by direct release of mediators from mast cells and basophils but direct mediator release occurs without evidence of a previous sensitization period, specific IgE antibodies, or antigen-antibody bridging on the mast cell/basophil cell membrane.¹⁰ Because anaphylactoid reaction is nonimmunologic it may occur the first time that the host is exposed to these agents. The reactions are of further interest because they can be elicited by small doses of the offending substance.¹⁰

Patients with asthma or urticaria are particularly prone to these reactions and in such individuals aspirin and cross-reactivity of several other NSAIDs have been documented to produce pseudo-allergic symptoms or simply to precipitate open asthmatic attacks.^{11–12}

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It has been calculated that between 8% and 20% of adult asthmatics experience bronchospasm after ingestion of aspirin and other NSAIDs.¹³ Anaphylactoid reactions to aspirin and other NSAIDs may even occur as a result of a distinct clinical syndrome also called aspirin-induced asthma in patients unaware of their intolerance.^{14–15} In particular, adverse reactions to KT have been reported in patients with a history of sensitivity to aspirin or to other NSAIDs^{16–17} but also in patients with no known sensitivity.^{12,18}

The authors report a case of fatal adverse reaction to KT in an asthmatic patient with no previously demonstrated hypersensitivity to aspirin or NSAIDs after an intramuscular injection. In this case, asthma was not solely responsible for the death of the patient. Pertinent information associated with this case is presented, along with additional findings of toxicological analysis.

CASE REPORT

The decedent was a 45-year-old white woman with a history of asthma. During acute asthmatic episodes, she treated and prevented bronchospasm with inhalers of salmeterol (Serevent), a long-term β_2 -agonist bronchodilator. A few weeks before death, she also suffered acute left wrist pain because of carpal tunnel syndrome. For the treatment of this acute pain, she received at home an intramuscular injection of 30 mg of KT (distributed in Italy as Lixidol, in the United States as Toradol). Shortly afterward, she felt unwell and within a few minutes, she suffered acute bronchospasm, collapsed, and became unconscious. On admission to the hospital emergency department, she was cyanotic and in full respiratory and cardiac arrest; resuscitative efforts were begun but in vain.

The autopsy was performed 48 hours after death and no significant pathologic findings were noted except the anatomic evidence of a recent asthma attack. Autopsy findings included mild coronary artery atherosclerosis and overinflated lungs with a few mucous plugs in the peripheral bronchioles. No angioedema of the larynx was observed. Microscopically, the bronchi showed muscular hypertrophy, basement membrane thickening, and wide fibrosis of the submucosa because of the airways remodeling process consistent with an asthmatic condition. Additional histologic findings included significant peribronchial inflammatory infiltrates composed of lymphocytes and eosinophils. Determination of serum IgE by paper radio-immuno-sorbent test and radio-allergo-sorbent test were performed approximately 2 weeks later because of technical problems. Unfortunately, the laboratory of clinical immunology was unable to perform reliable tests probably because of the effect of repeated freezing and thawing of samples with heavily hemolyzed plasma in the tubes. Also, the mast cell tryptase analysis failed because of the technical problems in the laboratory and the advanced autolysis of the postmortem blood. Other organs were macroscopically and histologically intact and the urine drug screen was negative.

Apart from the drugs administered during attempts at resuscitation, the toxicological analysis was also able to isolate and quantitate KT, which was found to be present in

the blood at a concentration of 1.9 $\mu\text{g/mL}$ but not its hydroxylated metabolites. The concentration of KT in this case was within the therapeutic range and was consistent with the administered dose of 30 mg. An acute overdosage with KT was indeed excluded in accordance with the time required for the analgesic to reach plasma peak levels. Official product information from Roche Pharmaceuticals, as noted in the 2005 edition of the Physicians' Desk Reference, provides approximate average pharmacokinetic parameters for Toradol (Lixidol in Italy) and indicates that the time to peak plasma concentration (T_{max}) has been calculated to occur within 44 ± 29 minutes for a single dose of 30 mg. Previous clinical trials reported also that peak levels of approximately 0.8 $\mu\text{g/mL}$ have been rapidly attained ($T_{\text{max}} = 0.8$ hours) after intramuscular administration.¹⁹

Based on the autopsy findings and the history in this case, including the timing of the symptoms in relation to the bronchospasm and subsequent collapse, death was attributed to an adverse reaction to KT, with asthma as an underlying contributing factor. The manner of death was classified as accident.

Toxicological Analysis

KT is a member of the pyrrolo-pyrrole group of NSAIDs and a 2-arylpropionate derivative which contains a chiral carbon in the β position of the propionate moiety. The mechanism of the drug seems to be mainly associated with the chiral S form.¹ KT, like many other polar NSAIDs, is likely to pass undetected in a routine basic or acidic/neutral drug screen using gas chromatography.²⁰ It is also difficult to isolate from biologic materials by liquid-liquid extraction methods because of its molecular properties. Solid-phase extraction methods for the isolation of KT from postmortem blood have been described.^{20–21} Methods previously reported for the analysis of KT from plasma^{22–24} are mostly based on a reversed-phase high-performance liquid chromatography with protein precipitation-direct injection method²⁵ and ultraviolet detection system.²¹ Gas chromatography-mass spectrometry, an instrumentation easily available in most forensic toxicology laboratories, has been also used for qualitative and quantitative analysis of KT after derivatization.²⁰

For the investigation of our case we used a solid-phase extraction method for the isolation of KT from postmortem blood and a gas chromatography-mass spectrometry for detection and quantitation of ketorolac, as trimethylsilyl derivative. Solid-phase extraction was performed with C_{18} column (500 mg/3 mL, J.T. Baker, Deventer, the Netherlands) following the producer indications. Agilent Technologies 6890 gas chromatograph equipped with mass selective detector 5975 (Agilent Technologies) was used. The mass selective detector was operated in the electron impact ionization mode with electron energy of 70 eV. Separation was achieved using a wall-coated open tubular fused silica CP-SIL (8. mt 15, i.d. 0.25 mm and film thickness 0.25 μm). Oven temperature was 100°C (hold time, 2.5 minutes), Δt 25°C/min till 290°C (hold time, 3 minutes). Helium gas was used at constant flow of 7 psi. The injection port and ion source were maintained at 270°C and 300°C, respectively.

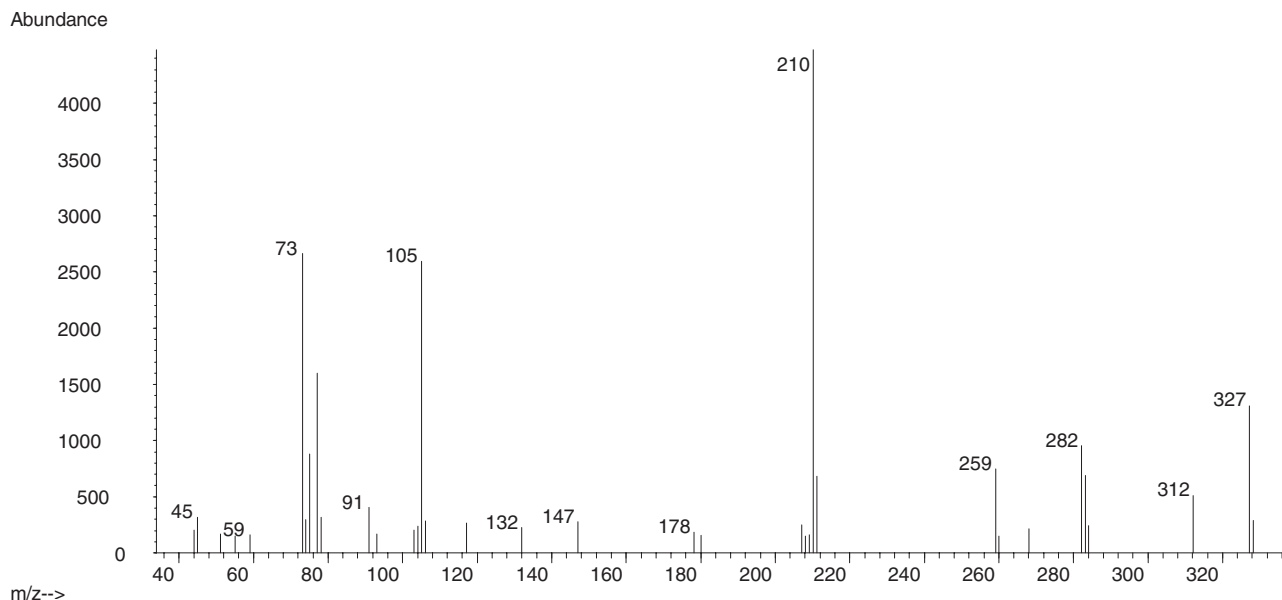


FIGURE 1. Mass spectrum of ketorolac-TMS.

For identification, full scan analysis was performed on first blood extract (0.5 mL) and solution of reference standard of ketorolac, both derivatized with bis-trimethylsilyl-trifluoroacetamide purchased from Sigma Aldrich Chemie GmbH, Germany. Full scan mass-to-charge (m/z) ratio range of 40 to 550 amu was selected.

Ketorolac, as trimethylsilyl derivative, was found, but no hydroxylated metabolites or conjugated forms were detected. For quantitative determination of KT, 0.5 mL of postmortem blood was spiked with 0.5 μg of internal standard (50 μL of ibuprofen, methanolic solution at 10 $\mu\text{g}/\text{mL}$ concentration) and mixed with 3.5 mL of distilled water. After centrifugation at 3500 rpm for 15 minutes, the solution was transferred to SPE- C_{18} column, activated with 2 mL $\times$ 3 of methanol and 2 mL $\times$ 3 of distilled water.

Elution of column was performed with 2 mL of methanol. The methanolic solution was evaporated to dryness under nitrogen flow. Dry extract was derivatized by silylation with 100 μL bis-trimethylsilyl-trifluoroacetamide, warming for 20 minutes at 90°C. One microliter of specimen was injected into gas chromatography/mass spectrometry system by autosampler (Agilent Technologies). Ketorolac standard (0.25–0.5–1–2 μg) and a blank sample were prepared with drug-free postmortem blood (0.5 mL) added of internal standard (0.5 μg of ibuprofen) and extracted in the same manner. Work solution of ketorolac (5 $\mu\text{g}/\text{mL}$) was obtained by scalar dilution in water of 148 μL of KT solution at the concentration of 10 mg/mL (Roche S.p.A, Milano, Italy).

Single ion monitoring analysis was performed, acquiring the following ion masses: ketorolac-TMS 210–282–327 m/z at retention time of 10.55 minutes; ibuprofen-TMS (internal standard) 160–263–278 m/z at retention time of 4.0000 minutes (Figs. 1 and 2). Calibration range (0–2 μg) has showed the reliability of the method with coefficient of correlation (r) of 0.9987.

Ketorolac concentration in blood of our case was calculated from linear regression of the calibrator response based on the peak area ratio (peak ketorolac-TMS to that of the internal standard-TMS). This concentration result was 1.9 $\mu\text{g}/\text{mL}$.

DISCUSSION

In this case, the combination of severe respiratory distress shortly after the intramuscular administration of KT, together with gross and microscopic evidence of acute bronchial asthma, provided enough evidence of an adverse reaction to KT. Death was attributed to an adverse effect of KT, resulting in an anaphylactic or anaphylactoid reaction with acute bronchospasm and cardiac arrest.

The resulting NSAID-related adverse events can be serious in certain patients for whom KT is indicated, especially when the drug is used inappropriately. In fact, KT is contraindicated in patients currently receiving aspirin or NSAIDs because of the cumulative risk of inducing serious NSAID-related side-effects and in patients with previously demonstrated hypersensitivity to KT or allergic manifestations to aspirin or other NSAIDs.¹ Therefore, healthcare professionals must be aware of the potential risks of anaphylaxis or pseudo-allergic reactions.

In literature, there is one report concerning an anaphylactoid reaction to KT in a 37-year-old man suffering acute left-sided chest pain with no previous history of allergies or risk factors. The patient developed facial swelling, shortness of breath, and chest tightness within 30 minutes from intramuscularly injection. The allergic symptoms resolved after a prompt intravenous administration of corticosteroid (methylprednisolone) and antihistamine (diphenhydramine), and the patient was discharged without medication after a 3-day hospitalization.¹⁸

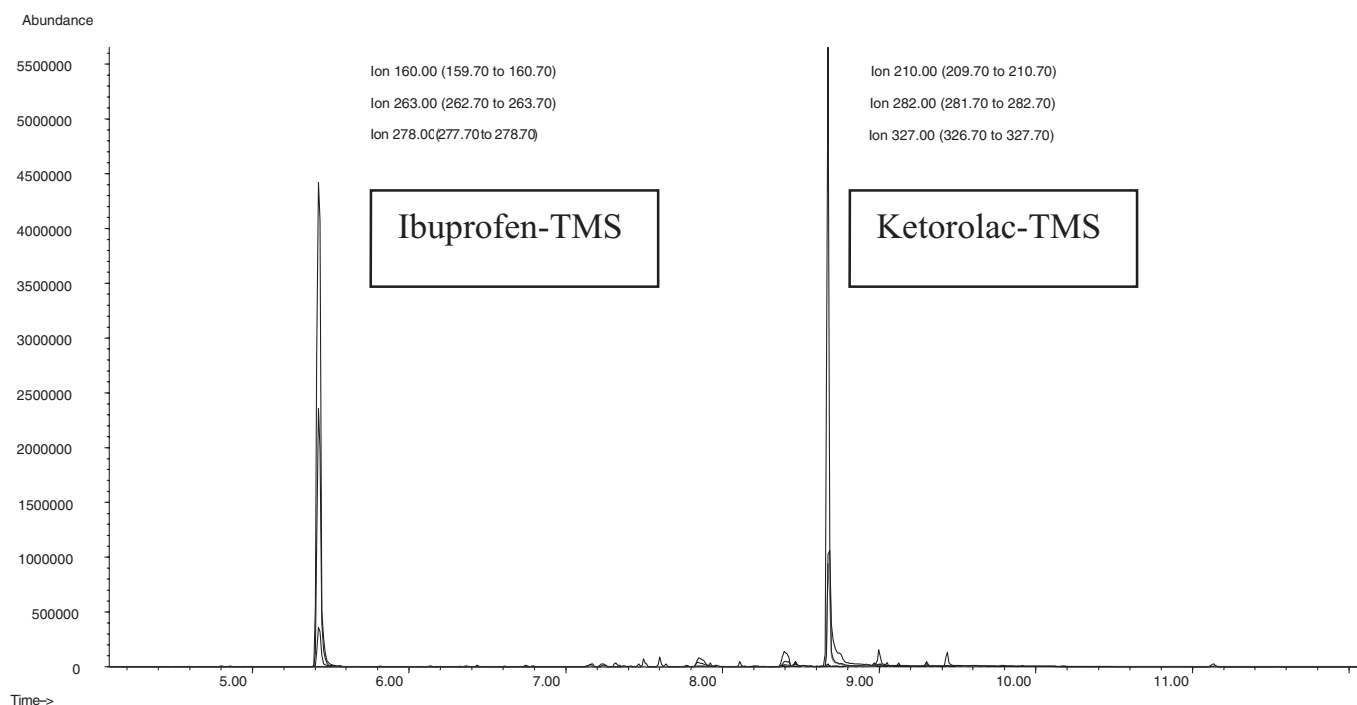


FIGURE 2. Single ion chromatogram of ketorolac-TMS from postmortem blood extract (0.5 mL).

In a similar case,²⁰ a 30-year-old white woman suffering acute lower back pain received an intramuscular injection of 60 mg of KT (Toradol). Shortly afterward, she felt unwell developing an apparent cardiac arrest, and entered ventricular fibrillation within 75 minutes after the administration. The cause of death was ruled as an acute anaphylactic drug reaction after the injection of Toradol. The drug was found to be present in the blood at a concentration of 2.9 mg/L which was within the therapeutic range and consistent with the administered dose of 60 mg.²⁰

Also in the case illustrated above, the concentration of KT found in postmortem blood (1.9 $\mu\text{g/mL}$) was within the therapeutic range and was consistent with the administered dose of 30 mg. An acute overdose with KT was indeed excluded. Such pathogenic hypothesis have to be made in any drug-related death according to the warnings reported for KT from Roche Pharmaceuticals (Physicians' Desk Reference, 2005) that increasing the dose of KT beyond the label recommendations does not provide better efficacy but can result in increasing the risk of developing serious adverse events.

However, even if there was no overdose, intolerance to analgesics is frequent and constitutes a major clinical problem, especially in some diseases such as asthma and urticaria. The clinical background of a patient often determines the type of adverse response to an analgesic¹² as in this case where the victim suffered acute asthmatic episodes and treated them with inhalers. In several cases, the symptoms suggest an allergy or a systemic anaphylaxis in which an immunologic mechanism is present. However, in many other cases physicians faced with nonimmune (non-IgE-mediated)

reactions because of such events can rarely be traced to reactions between the drug and a specific antibody or sensitized T-lymphocytes.¹²

Anaphylactic and anaphylactoid drug-induced reactions are of particular interest for the forensic pathologist because of the very few postmortem findings among which the only evidence can be represented by toxicological analysis and allergy testing. In fact, in many cases of fatal anaphylaxis or anaphylactoid reactions, no specific macroscopic findings are present at postmortem examination. This reflects the rapidity and mode of death, which is often the result of shock.²⁶

Regarding the allergy testing, it has been proposed that an increase of postmortem serum tryptase level be used to establish anaphylaxis as a cause of death.²⁷ However, it should be clearly noted that postmortem increase of serum tryptase concentrations is not a specific finding, therefore, cannot be considered diagnostic of an anaphylactic death.¹⁰ In fact, there are reports detailing nonanaphylactic deaths exhibiting increased postmortem serum tryptase levels.^{28–30} Thus, the presence of an increased postmortem tryptase level cannot be considered pathognomonic for a death caused by anaphylaxis or an anaphylactoid event.¹⁰ Neither can an absence of an increased postmortem tryptase level be considered sufficient to rule out anaphylaxis or an anaphylactoid event as the cause of death.²⁸ In fact, elevated levels of serum tryptase may not be detected during the first 15 to 30 minutes after the onset of anaphylaxis or in people experiencing rapidly fatal anaphylaxis.^{27,31} However, elevations in the postmortem tryptase remain an important supporting finding

in the diagnosis of anaphylactic and anaphylactoid deaths (AADs) but it should not be used alone.²⁶

Tests for specific IgE and mast cell tryptase together might help to determine whether AADs occurred. These tests should be performed in all cases with a suggestive clinical history and no specific findings at necropsy.²⁶ In fact, analyses of total IgE and specific IgE by paper radio-immunosorbent test and radio-allergo-sorbent test are also possible in postmortem serum but they can merely verify the atopic disposition and the degree of sensitization of the patient.²⁹ Also, there are no readily available IgE tests for all relevant allergens or drugs and tests for specific IgE antibodies do not always provide conclusive evidence of the cause of anaphylaxis.^{10,26} Therefore, the results of these assays (even if unavailable as in this case because of technical problems) need to be interpreted in the context of clinical history (which usually takes precedence over diagnostic tests as it can be the most important tool to establish the cause of immune and nonimmune reactions) and postmortem findings.¹⁰

In particular, it is well known that allergic mechanisms for aspirin-like drug-induced asthma have also been excluded by extensive immunologic studies.^{9,32} In certain individuals, analgesics can produce anaphylactic reactions, probably through an immunologic mechanism. In some asthmatics, such drugs can only precipitate bronchoconstriction inducing a severe asthma attack, probably through inhibition of bronchial cyclo-oxygenase which leads to an imbalance of prostanoids in the respiratory tract.³³

Inhibition of prostaglandin synthesis through blockade of the cyclo-oxygenase pathway of arachidonic acid metabolism is probably responsible for both the beneficial and the toxic effects of the drug. The cyclo-oxygenase enzymes, in fact, act upon arachidonic acids to produce prostaglandins and thromboxanes (prostanoids) which are potent pro-inflammatory mediators.³⁴ Therefore, the inhibition of cyclo-oxygenase by NSAIDs lowers the synthesis of prostanoids producing analgesia but also increases the products of lipoxygenase pathway such as leukotrienes (LTs). Lipoxygenase enzymes convert arachidonic acid into LTs which are lipid mediators in inflammation and allergy and highly potent bronchoconstrictors of small and large airways with chemiotactic activity.³⁵ Some of the major signal molecules responsible for asthma attacks are indeed the leukotrienes.^{36–37} Moreover, drugs that interfere with the biosynthesis and action of LTs have been proposed as novel medications in the treatment of asthma and allergic rhinitis.^{38–39} Such pathogenic mechanism, however, does not explain why NSAIDs can provoke a fatal bronchospasm in only a few asthmatic patients whereas most of them are not affected by such drugs or even aspirin. Further research studies are still needed in this matter.

Anti-inflammatory drugs that may precipitate asthma attacks include indomethacin, mefenamic acid, flufenamic acid, cyclofenamic acid, ibuprofen,^{33,40} fenoprofen,³³ ketoprofen,⁴¹ naproxen,⁴² diclofenac,⁴³ aminopyrine,⁴⁴ sulfapyrazone,⁴⁵ phenylbutazone, piroxicam, sulindac,⁴⁶ tiaprofenic acid, zomepirac,⁴⁷ tolmetin, and⁴⁸ diflunisal.^{7,49} Asthma caused by topical application of KT has also been reported.¹⁷

Although asthma is, by definition, a reversible condition, it can also be lethal, thus, representing another form of sudden death to be analyzed.^{50–51} However, a wide variety of substances can precipitate bronchospasm influencing the fatal outcome of an asthmatic attack.⁵² It is currently recognized that in patients with bronchial hyper-responsiveness there is an abnormal sensitivity to a wide range of stimuli such as cold air (especially during exercise), irritant chemicals (including allergens), stimulant drugs, and so on. Therefore, the physician has to keep in mind that in asthmatic patients, bronchospasm can be induced by drugs among which NSAIDs and certain analgesics are the most common and death may have an iatrogenic cause.

The rapidity with which the symptoms developed in the patients affected by an adverse reaction to NSAIDs generally reflects the time required for such prescription drugs to begin the analgesic and/or anti-inflammatory effects. Specifically for KT, based on the official product information, it is within 30 minutes with maximum effect in 1 to 2 hours after intravenous or intramuscular administration. Finally, in the case of the young lady, based on the context of clinical history (see asthmatic episodes treated with inhalers in the past), timing and symptoms suffered shortly after intramuscular injection (see acute bronchospasm), the autopsy findings (evidence of a recent asthma attack), and the drug concentration in the decedent's blood (within the therapeutic range and consistent with the administered dose), provided enough evidence that the cause of death was KT-induced bronchospasm with asthma as a contributory factor. Therefore, death was attributed to an adverse effect of KT, resulting in anaphylactic or anaphylactoid reaction with acute bronchospasm and cardiac arrest, with underlying asthma.

The manner of death determination in this case might be controversial for some. However, it was classified as accident in accordance with the NAME guidelines for manner of death classification,⁵³ as deaths caused by drug-induced anaphylaxis or anaphylactoid reaction are often sudden, unpredictable, and involve an external factor as in the present case.

CONCLUSION

KT can lead to a severe aggravation of asthma along with allergic (anaphylactic) or allergic-type (anaphylactoid) reactions. The occurrence or aggravation of asthma or an episode of anaphylactic or anaphylactoid reaction in patients for whom NSAID treatment is indicated, should always be kept in mind especially in asthmatic patients or individuals with a previous history of allergies or previously demonstrated hypersensitivity to NSAIDs or aspirin. Such adverse reaction to similar drugs, however, can also occur in patients with no known hypersensitivity.

A careful and complete review of the clinical history is always mandatory in suspected anaphylactic or anaphylactoid episodes related to drugs and the results of allergy testing might be useful in making the diagnosis or distinguishing them from other entities. However, sometimes diagnosis of adverse reaction to drugs can still be made, or at least suggested by forensic pathologists, even without the benefi-

cial support of tryptase and IgE testing, based on timing, symptoms, postmortem findings, and the clinical history which can be the most important tool to establish the cause of immune and nonimmune reactions.

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