These meats are horse meat: 6% of horse carcasses marketed for human medicine but is still widely used in the veterinary field. Today, PBZ is no longer marketed for human medicine, and pathology is named “idiopathic” SJS-TEN. Major drugs responsible of these reactions are some nonsteroidal anti-inflammatory drugs (NSAIDs) (Mockenhaupt et al., 2008; Roujeau et al., 1995). In the 1990s, NSAIDs represented 38% of culprit drugs. Phenylbutazone (PBZ) was found in 55% of cases (Guillaume et al., 1987). Today, PBZ is no longer marketed for human medicine but is still widely used in the veterinary field (Dubreil-Cheneau et al., 2011). Recently, this drug was banned from food in Europe after fraud related to horse meat: 6% of horse carcasses tested in 2012 were positive for PBZ (ec.europa.eu, 2013). These meats are consumed by humans. PBZ and oxyphenbutazone (OPB), its major active metabolite (Lees et al., 1986; Lees and Toutain, 2013; Tobin et al., 1986), or suxibuzone (SBZ), a PBZ prodrug usually used in veterinary medicine, could be found in individuals who consumed meat and milk containing PBZ. Because susceptible individuals could then develop SJS/TEN, our objective was to quantify drug-induced SJS-TEN, who were compared with 33 patients (20 women) treated for drug-induced SJS-TEN. Seven patients (five women), treated for idiopathic SJS-TEN were included: one patient without drug intake at all during the month before the start of SJS-TEN and six patients with a drug intake during the month before the start of symptoms that was possibly, unlikely, or very unlikely related to the reaction, based on an ALDEN score of 3 or less. They were compared with 33 patients (20 women) treated for drug-induced SJS-TEN. In this group, drugs responsible were allopurinol (n = 7), lamotrigine (n = 10), nevirapine (n = 9) and sulfamethoxazole (n = 7). Demographic and clinical data are described (Table 1). All plasma samples were analyzed by liquid chromatography coupled with mass spectrometry (QuantumUltra, ThermoFisher, San Jose, CA) using an electrospray ionization in negative mode. Specific multiple reaction mode parameters were 307.13/278.9 (130.9) for PBZ, 323.13/295.0 (134.0) for OPB, and 437.14/306.8 (130.7) for SBZ. The standard concentrations ranged from 0.01 to 5 mg/L. The method validation was based on the quantification of the drug in plasma and blister liquid.

Are Idiopathic Stevens-Johnson Syndrome/Toxic Epidermal Necrolysis Related to Drugs in Food? The Example of Phenylbutazone

TO THE EDITOR

Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are rare life-threatening mucocutaneous reactions associated with a high mortality risk (8–23%, according to hospital centers) (Duong et al., in press; Sekula et al., 2013). SJS and TEN are drug-related reactions for approximately two thirds of SJS-TEN patients (Sassolas et al., 2010). For 36% of patients, no culprit drug is clearly identified, and pathology is named “idiopathic” SJS-TEN. Major drugs responsible of these reactions are some nonsteroidal anti-inflammatory drugs (NSAIDs) (Mockenhaupt et al., 2008; Roujeau et al., 1995). In the 1990s, NSAIDs represented 38% of culprit drugs. Phenylbutazone (PBZ) was found in 55% of cases (Guillaume et al., 1987). Today, PBZ is no longer marketed for human medicine, and pathology is named “idiopathic” SJS-TEN. Major drugs responsible of these reactions are some nonsteroidal anti-inflammatory drugs (NSAIDs) (Mockenhaupt et al., 2008; Roujeau et al., 1995). In the 1990s, NSAIDs represented 38% of culprit drugs. Phenylbutazone (PBZ) was found in 55% of cases (Guillaume et al., 1987). Today, PBZ is no longer marketed for human medicine, but is still widely used in the veterinary field (Dubreil-Cheneau et al., 2011). Recently, this drug was banned from food in Europe after fraud related to horse meat: 6% of horse carcasses tested in 2012 were positive for PBZ (ec.europa.eu, 2013). These meats are clearly identified and (ii) patients with drug-induced SJS-TEN, who were control subjects according to the same protocol and guidelines, for whom one culprit drug was clearly identified thanks to algorithm of drug causality for epidermal necrolysis (ALDEN) score considered as probable or very probable (score ≥ 4). Seven patients (five women), treated for idiopathic SJS-TEN were included: one patient without drug intake at all during the month before the start of SJS-TEN and six patients with a drug intake during the month before the start of symptoms that was possibly, unlikely, or very unlikely related to the reaction, based on an ALDEN score of 3 or less. They were compared with 33 patients (20 women) treated for drug-induced SJS-TEN. In this group, drugs responsible were allopurinol (n = 7), lamotrigine (n = 10), nevirapine (n = 9) and sulfamethoxazole (n = 7). Demographic and clinical data are described (Table 1). All plasma samples were analyzed by liquid chromatography coupled with mass spectrometry (QuantumUltra, ThermoFisher, San Jose, CA) using an electrospray ionization in negative mode. Specific multiple reaction mode parameters were 307.13/278.9 (130.9) for PBZ, 323.13/295.0 (134.0) for OPB, and 437.14/306.8 (130.7) for SBZ. The standard concentrations ranged from 0.01 to 5 mg/L. The method validation was based on the quantification of the drug in plasma and blister liquid.

**Abbreviations:** LLOQ, lower limit of quantification; NSAID, nonsteroidal anti-inflammatory drug; OPB, oxyphenbutazone; PBZ, phenylbutazone; SBZ, suxibuzone; SJS, Stevens-Johnson syndrome; TEN, toxic epidermal necrolysis

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on the international recommendations. Chromatogram profiles of the lower limit of quantification (LLOQ) and the highest calibrator are presented and compared with a chromatogram issued from a patient sample (Figure 1). Signals of all patients’ samples included were only 50- to 350-fold lower than the LLOQ (0.01 mg/L). The limit of detection was 0.5 µg/L. Our method was sensitive and used the LLOQ that is recommended by international authorities for research on animals for food.

All samples from patients treated for idiopathic SJS-TEN were undetectable for PBZ: PBZ accumulation from food could not explain these cases of SJS-TEN. In parallel, PBZ was also undetectable in the drug-induced group, members of which could present with several causes of SJS-TEN (drug and dietary origins). Moreover, OPB, which has greater tissue diffusion (Lees et al., 1986), and SBZ were not detectable in both groups.

During our period of inclusion, PBZ was still used in human medicine, but none of our patients received it. PBZ dosage was targeted because it is the most commonly used NSAID in equine orthopedics around the world. PBZ also has good diffusion (Gaucher et al., 1983) in different tissues (muscles, milk) and is used in multiple animals (horses, cow calves) (Arifah and Lees, 2002; Tobin et al., 1986). As a consequence, it could have been accumulated in humans who consume large quantities of meat and milk. However, some major species differences are reported concerning its pharmacokinetic parameters: PBZ terminal elimination half-lives are 5 hours in horses, 53 hours in calves, and 50–105 hours in humans (Lees et al., 1987). These data suggest the potential risk for PBZ and OPB accumulation in humans, but despite these characteristics, these drugs were not detected in samples of patients. Despite the negative results on liquid chromatography-mass spectrometry, no definitive conclusions can be made. Reasons are as follows: (i) Times between slaughter and meat consumption and between blood taking from last meat or milk exposure were not reported. These variables may result in false negativity. (ii) Dietary exposure of idiopathic patients to meat and milk found to have occult PBZ is unknown. (iii) More fundamentally, it needs to be proven that meat containing PBZ results in accumulation of PBZ elevated serum concentrations in humans who consume them. Lees and Toutain (2013) estimate that the risk of PBZ accumulation from food is unlikely because ingested amounts of meat and/or milk would be significant. To date, the relationship between concentration of the culprit drug and occurrence of SJS-TEN has been shown only for fixed drug eruption (Duong et al., in press).

The prospects of this study are to investigate other drugs found in human food and likely to induce SJS-TEN, particularly oxicams, widely used in human and veterinary medicines. It will be also essential to highlight the correlation between

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Patients with Idiopathic SJS-TEN (n = 7)</th>
<th>Control Subjects: Patients with Drug-Induced SJS-TEN (n = 33)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women, n (%)</td>
<td>5 (72)</td>
<td>20 (61)</td>
</tr>
<tr>
<td>Mean age in years, M ± SD (range)</td>
<td>42.1 ± 23.2 (21–78)</td>
<td>48.2 ± 24.8 (6–87)</td>
</tr>
<tr>
<td>Mean SCORTEN, M ± SD (range)</td>
<td>0.6 ± 0.8 (0–2)</td>
<td>0.9 ± 1.0 (0–3)</td>
</tr>
<tr>
<td>Percentage mean detachment area, M ± SD (range)</td>
<td>18.0 ± 11.7 (2–35)</td>
<td>19.3 ± 23.3 (2–100)</td>
</tr>
<tr>
<td>Deaths, n</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Mycoplasma infections</td>
<td>4 without infection</td>
<td>7 without infection</td>
</tr>
<tr>
<td></td>
<td>3 unknown status</td>
<td>26 unknown status</td>
</tr>
</tbody>
</table>

Abbreviations: M, mean; SD, standard deviation.

Table 1. Demographic and clinical data of patients included in the study (N = 40)

Figure 1. Typical chromatographic profiles of diclofenac, the internal standard, and PBZ, OPB, and SBZ. (a) The highest 5-mg/L calibrator, (b) the lowest 0.01-mg/L calibrator, LLOQ, and (c) a plasma patient. The representation in relative abundance of the total signal is the reason why we observe peaks for each analyte. However, areas of the sample in b are 51-, 339-, and 77-fold higher than those of the patient sample, respectively, for PBZ, OPB, and SBZ. LLOQ, lower limit of quantification; min, minutes; OPB, oxyphenbutazone; PBZ, phenylbutazone; SBZ, suxibuzone.

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the onset of cutaneous symptoms of the disease and the plasma and tissue concentrations of drug-induced SJS-TEN.

In conclusion, no trace of PBZ and its metabolite were found in the plasma of 40 patients presenting with idiopathic or drug-induced SJS-TEN.

CONFLICT OF INTEREST
The authors state no conflict of interest.

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REFERENCES


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TO THE EDITOR

Trichodosplasia spinulosa polyomavirus (TSPyV) has recently been identified as the probable etiological agent of trichodosplasia spinulosa, a rare and severe proliferative skin disorder observed in immunocompromised patients, especially children (Rouanet et al., 2016; van der Meijden et al., 2010). Recent serological studies have indicated that TSPyV infection is common and that TSPyV seroprevalence increases rapidly with age from childhood to reach approximately 70–90% in adults in blood donors and in populations of hospitalized patients in Europe, Australia, and Japan (Chen et al., 2011; Fukumoto et al., 2015; Nicol et al., 2013; Sroller et al., 2016; van der Meijden et al., 2013). However, seroprevalence data are lacking for other populations, and the routes by which this virus is transmitted and acquired remain unknown. This work aims to obtain new insight into the modes of distribution and acquisition of TSPyV from family-based epidemiological analyses in African populations.

This study was carried out on two populations from Cameroon, Central Africa, in which we previously reported epidemiological studies searching for intrafamilial transmission of human

Trichodosplasia Spinulosa Polyomavirus Infection Occurs during Early Childhood with Intrafamilial Transmission, Especially from Mother to Child


TO THE EDITOR

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