American Association of Poison Control Centers Database Characterization of Human Tilmicosin Exposures, 2001–2005

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ABSTRACT

Background: Tilmicosin is a veterinary antibiotic with significant human toxicity at doses commonly used in animals, but the parenteral dose-response relationship has not been well characterized.

Methods: Human exposures to tilmicosin in the database of the American Association of Poison Control Centers (AAPCC) from 2001 to 2005 were analyzed for demographic associations, exposure dose, clinical effects and outcomes.

Results: Over the 5-year period, there were 1,291 single-substance human exposures to tilmicosin. The mean age was 39.1 years, and 80% were male. By route there were 768 (54%) parenteral exposures. Patients with parenteral exposures had a significantly increased likelihood of being seen at a healthcare facility, admission, and admission to an ICU. With nonparenteral exposure, most had no clinical effects or minor effects, and there were no major effects or deaths. With parenteral exposure, moderate effects occurred in 46 (6%), major effects in 2 (0.3%) and there were 4 (0.5%) deaths, two of which were suicides. A dose-response relationship could be demonstrated. Clinical effect durations of up to a week occurred at even the lowest dose range.

Conclusions: Over 250 cases of human tilmicosin exposure are reported to poison centers per year and over 150 of those are parenteral. Most exposures produce no or minor effects, but fatalities have occurred with parenteral exposure. The case fatality rate in parenteral exposures is 10 times the case fatality rate for all human exposures in the AAPCC database. Significant adverse and prolonged effects are reported at parenteral doses <0.5 mL, suggesting that all parenteral exposures should be referred for healthcare facility evaluation.

BACKGROUND

Although exposure to tilmicosin (Micotil 300), a veterinary macrolide antibiotic, has demonstrated significant human toxicity at doses used in animals, the human dose-response relationship, particularly with parenteral exposure, has not been well characterized. A previous preliminary study of human exposures

in the American Association of Poison Control Centers (AAPCC) database demonstrated various demographic, clinical-effect, and outcome associations and attempted a dose-response analysis of parenteral exposures [1]. However, that study did not validate the exposure dose. Because tilmicosin is a liquid, determination and documentation of dose is subject to various inaccuracies. This

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study expanded the time range of the previous study and validated doses with the reporting poison centers in order to better characterize the dose-response relationship in exposures by various routes.

METHODS

The national database of the AAPCC was searched from 2001 through 2005 for all human exposures to tilmicosin. Single-substance tilmicosin exposures were included and analyzed by patient age and gender, exposure route, exposure reason, substance amount, clinical effects, medical outcome, effects duration, and therapy. Doses of exposure were validated by contacting reporting poison centers and having the amounts documented in the notes field correlated with the coded dose amount. Only validated cases were included in the dose-response analysis. Tilmicosin comes as a single preparation of 300 mg/mL. Parenteral exposures were analyzed in dose quintiles of 0.01–0.49 mL, 0.5–1 mL, 1.1–5 mL, 5.1–10 mL, and 10.1–15 mL, as well as in mg/kg when patient weight was known. Statistical analysis of variable differences was by two-tailed Fisher Exact test, Chi Squared test, Student T-test, and Odds Ratio (using the approximation of Woolf) where appropriate and was performed using GraphPad InStat 3.06 for Windows 95 (GraphPad Software, San Diego,CA, www.graphpad.com).

RESULTS

Over the 5-year period, there were 1,291 single-substance human exposures to tilmicosin reported to US poison centers, or an average of 258 per year. The mean age was 39.1 years (range, 18 months–81 years; median, 40 years) and 80% were male. Of these exposures, 99.5% were acute. There were 10 (1%) adverse drug reactions, one intentional misuse, 10 (1%) intentional suicides, and 1266 (98%) unintentional exposures. More than 40% of unintentional exposures were coded as occupational or as occurring in the workplace. Of the initial calls to the poison center, 25% originated at a healthcare facility (HCF) and 75% at a residence, workplace, or other non-HCF site.

By route there were 264 (20%) dermal, 291 (22.5%) ingestion, 71 (5.5%) ocular, 768 (54%) parenteral, and small numbers of other or unknown routes of exposure (numbers sum to >100% because of multiple routes of exposure in individual cases). Of these cases, 45% were managed at a HCF, with a significantly increased likelihood of parenteral exposures being seen at a HCF, admitted, and admitted to an ICU than nonparenteral exposures (Table 1).

Most patients had no effects or minor effects by nonparenteral routes (Table 2). There were no major effects or deaths by any of these routes. (See Appendix B for AAPCC Outcome definitions.)

With parenteral exposure, 99% of patients were 12 years or older; 81% were male. Because patient weight is not a required field in the AAPCC database, there were only 12 patients who had

Table 1: Parenteral versus Nonparenteral Exposures, by Management Site			
n = 1442	Nonparenteral	Parenteral	Significance
Exposures	48%	59%	
Managed in HCF	37%	50%	p < 0.0001; OR 1.668; 95%CI 1.329–2.095
Admitted	3.6%	9.8%	p < 0.0001; OR 2.877; 95%CI 1.716–4.821
Admitted to ICU	1.2%	5.6%	p < 0.0001; OR 5.120; 95% CI 2.163–12.1222

Table 2: Outcomes by Route					
Route	No/minimal Effect	Minor	Moderate	Major	Death
Dermal	168 (64%)	86 (33%)	7 (2.7%)	—	—
Ingestion	207 (71%)	72 (25%)	7 (2.4%)	—	—
Ocular	34 (48%)	36 (51%)	1 (1.4%)	—	—
Parenteral	134 (17%)	470 (61%)	46 (6%)	2 (0.3%)	4 (0.5%)

a parenteral exposure for whom both patient weight and the dose in mL were available. With parenteral exposure, moderate effects occurred in 46 (6%), major effects in 2 (0.3%), and there were 4 (0.5%) deaths (Figure 1). Two of the 4 deaths were suicides. When patient weights were not available, higher parenteral doses in mL were associated with more serious outcomes, including death at the doses ≥10 mL (Figure 2). When patient weight and dose were available, the mean dose in mg/kg for exposures coded as having “moderate effects” was significantly higher (p = 0.0323; two-tailed t-test) than that for “minor effects” (Figure 3).

There was sparse documentation of specific clinical effects. The most commonly coded clinical effect in parenteral exposures was pain/irritation at the injection site in 19% of patients. Systemic symptoms coded in 1% or greater of patients included cardiovascular (chest pain 1%, hypotension 1%, tachycardia 2%), and neurological (headache 1%, numbness 1%) effects.

Clinical effects durations of up to a week occurred at even the lowest dose range (0.1–0.49 mL). (Figure 4)

Overall duration of effects by route of exposure is summarized in Table 3.

No dose-response relationship could be demonstrated for dermal, ingestion, or ocular exposures secondary to the low numbers of outcomes greater than minor and the paucity of dose and weight documentation.

DISCUSSION

Tilmicosin is a macrolide antibiotic administered subcutaneously to cattle to prevent or treat bovine respiratory tract disease.

Figure 1: Outcomes by exposure route. Major effects and death were only seen with parenteral exposure.

Figure 2: Dose-response relationship in parenteral tilimicosin exposure, outcome by dose in mL.

Tilimicosin has an elimination half-life of 29.4 hours in cattle and 34.6 hours in sheep. Time to peak serum concentration after SC administration was 0.5 and 3.9 hours in cattle and sheep, respectively [2].

Demographics

In this study, there were >250 cases of human exposure to tilimicosin a year reported to poison centers in the US; more than 150 of these (54%) were by the parenteral route. Other routes of expo-

sure included 20% dermal, 22.5% ingestion, and 5.5% ocular. Similarly, in a review of 46 unintentional human exposures reported to Texas poison centers from 1998 through 2003, 48% were via parenteral exposure [3]. A retrospective review of 3,168 reports of human exposure to Micotil 300 to the Elanco Animal Health Pharmacovigilance Unit between March 1992 and March 2005, found that 61% were due to accidental self injection, with the remainder dermal (17%), oral (17%), ocular (2.6%), and inhalation (0.1%) [4].

Figure 3: Outcomes by mean dose of parenteral exposure, in mg/kg (n = 12).

Figure 4: Duration of clinical effects by parenteral dose quintile, in mL.

Table 3: Effects duration by route

Route	≤2 hr	≤8 hr	≤24 hr	≤3 days	≤1 wk	<1 mo
Dermal*	39 (47%)	16 (19%)	9 (11%)	16 (19%)	1 (1%)	1 (1%)
Ingestion	39 (52%)	21 (28%)	9 (12%)	5 (7%)	—	1 (1.3%)
Ocular	24 (37%)	8 (22%)	1 (3%)	2 (6%)	—	1 (3%)
Parenteral	146 (36%)	76 (19%)	88 (22%)	82 (20%)	13 (3%)	1 (<1%)

*One case with anticipated permanent injury

Clinical effects

In this study, 75% of all patients exposed to tilmicosin and >80% of parenterally exposed individuals became symptomatic, with the most common documented complaint of pain/irritation at the injection site. In the Texas poison center study, the most common effects were also local injection site pain and irritation [3]. The review of 3,168 reports of human exposure to Micotil 300 by Veehuizen found at least one symptom in 44% of exposed individuals by all routes. In that series as well, the most commonly reported complaints in the patients who had accidental self-injection were local effects, including injection site pain, bleeding, and inflammation [4]. In another series, all 26 patients with injection injury, in a case series of 36 accidental human tilmicosin exposures in Canada from March 1991 through August 1993, complained of local effects at the injection site including pain, bleeding, redness, itching, and/or swelling [5].

In this study, systemic effects were much less commonly reported and/or recorded, but complaints of chest pain, hypotension, and tachycardia were among the most frequently coded significant clinical effects with parenteral exposure. In the Texas poison center series, only 1 patient in the parenteral group was noted to have tachycardia and hypertension (neither defined), and 2 had "neurological effects" and headache. One patient in the nonparenteral exposure group was noted to have "cardiovascular" complaints—chest pain and ECG changes—none of which are further detailed. Route of exposure was not reported in this patient, and volumes or dosages of possible exposure for any of the patients are unavailable in this case series [3]. In the Veenhuizen report, systemic effects were also less commonly reported but included nausea, tachycardia (rate not defined), and dizziness, each at 3%. Anxiety, abnormal taste, headache, light-headedness, parasthesias, and chest pain were reported at a rate of 2% each. Hypertension (not defined), weakness, vomiting, and nervousness were each reported with a frequency of 1%, although the poison center database does not record the time to onset of symptoms; in the Veenhuizen report, time to onset of symptoms ranged from <15 minutes to >24 hours. In those patients for whom time to onset was known (62), 56% had clinical signs within 60 minutes of exposure [4].

In sheep and cattle, at appropriate dosing and route of administration there were no statistically significant abnormalities in any cardiovascular parameters (blood pressure, heart rate, MAP, or respiratory rate) [2]. However, studies with dogs and cattle have revealed significant cardiovascular effects when tilmicosin is administered at doses >10 mg/kg, or by other routes (IM, IV, IP) [6,7]. Hypotension is probably a direct result of negative inotropic effects on the heart via interference with calcium cycling at the level of the sarcoplasmic reticulum, inhibiting calcium flux across membranes [8], and depletion of intracellular calcium. Many other macrolide antibiotics have been shown to have effects on myocardial calcium channels. This antagonism of calcium channels leads to negative inotropic effects that can be mitigated by the administration of high doses of exogenous calcium [9]. Others theorize a contribution to cardiovascular toxicity

from stimulation of cardiac beta receptors [6], but this is in dispute given that the administration of a beta-blocking agent did not attenuate tilmicosin-induced tachycardia in a dog study [7]. Tachycardia seen with tilmicosin toxicity may be secondary to the direct effect of atrial stretch on the sino-atrial node and in response to the increase of left ventricular end diastolic pressure [7]. Given that there was no attenuation of this effect by the administration of a beta antagonist (propranolol) to tilmicosin-poisoned dogs, this effect is not likely mediated, or at least entirely mediated via direct beta stimulation. In fact, administration of propranolol to the dogs in that study exacerbated the toxic effects of tilmicosin. Another contributing factor may be a decrease in parasympathetic tone as a reflexive response to the fall in pulse pressure and mean arterial pressure (MAP). Other macrolide antibiotics have been theorized to contribute to hypotension by stimulating histamine release [10]. Facial swelling and itching has been reported in test animals administered tilmicosin [7] and other studies have shown histamine release after administration of the macrolides erythromycin, leucomycin, oleandomycin and spiramycin [10]. A study in dogs demonstrated *in vitro* erythromycin on dog Purkinje cells induced prolongation of cardiac action potentials and had class 1A antidysrhythmic activity. It also delayed repolarization, in a dose-dependent fashion, explaining its ability to produce prolongation of the QT in a dose-dependent fashion [11].

Thus, the cardiovascular effects are likely multifactorial in etiology. Further, animal studies demonstrate that the route of administration is exceedingly important in determining cardiovascular toxicity. Cattle can tolerate 5-fold overdose if the drug is administered SC. Intravenous dosing in cattle, sheep, horses, swine and goats, however, produced significant toxicity, including death, at 5–30 mg/kg, depending on species [3].

Deaths

In this study, there were four deaths, two of which were suicides. The case-fatality rate of 0.5% in parenteral exposures is 10-fold higher than for all substance exposures in the AAPCC database. The AAPCC database does not include case notes and thus clinical presentations and courses are not known. In the Veenhuizen study, there were 2 accidental and 11 cases of intentional exposure to tilmicosin that resulted in death (case-fatality rate 1.1%). The majority of these were by IV or IM injection, but the route of exposure was unknown in 4 patients. Seven intentional exposure patients survived. Clinical scenarios prior to death were also not available for most patients, as many were reported as found collapsed, unconscious, or dead. In 2 cases, patients developed vomiting, dysrhythmias, and chest pain leading to cardiac and respiratory arrest. Descriptions of any resuscitative efforts were not included [4].

Several case reports of death have been reported from both intentional and accidental parenteral exposures to tilmicosin. One case report also implicated the propylene glycol diluent of the tilmicosin as at least a contributing factor in the patient's death. The amount of propylene glycol injected was estimated at 17 mg/kg along with approximately 21 mg/kg of

tilmicosin. In this intentional injection the patient was found to have a blood tilmicosin level of 30 ppm (noted as “markedly elevated” but no reference range provided) on postmortem examination [12].

Other case reports in the literature describe systemic effects and ECG abnormalities [12–14]. In one well-described case report [13], a previously healthy 28-year-old farm worker had an unintentional exposure to <5 mL (maximum possible dose 1800 mg) tilmicosin by injection into his arm. Severe symptoms developed approximately 5 hours later, which included chest pain and ECG abnormalities including sinus tachycardia, premature ventricular contractions, intraventricular conduction delay with incomplete right bundle branch block, and inversion of T waves in inferior leads. The patient was treated with sublingual nitroglycerin and intravenous morphine with minimal relief of his chest pain. Laboratory abnormalities during his hospital course included hypokalemia at 2.9–3.2 mmol/L (3.5–4.5), and mildly elevated CK of 298 (ref 24–204 IU/L) and CK-MB percent of 2.6. Serum troponin measurements remained negative. Chest pain resolved and no dysrhythmias were noted throughout the remainder of his hospital stay. Post-hospitalization, his ECG had completely normalized and he had no medical sequelae.

Clinical effect durations

In this study, clinical effects from parenteral exposure of up to a month were reported and durations of up to a week were seen with exposures <0.5 mL. Prior to this, there has been no systematic characterization of the duration of clinical effects from parenteral exposure. Crown et al [14] state that their patient subjectively reported his “lungs just haven’t been the same since” and complained of decreased exercise tolerance 4 weeks after exposure. There was no comment regarding persistent ECG changes, although all evidence of toxicity was reported as resolved at the time of discharge. Neither the Texas [3] nor the Canadian case series [5], commented regarding duration of clinical or ECG effects.

Dose response

In this study, a dose-response relationship could be seen between the total dose in mL and/or the dose in mg/kg and clinical outcomes. Minor effects were reported even with injection amounts <0.5 mL. When dose and weight were known, patients with minor effects had a mean injection dose of approximately 2 mg/kg (~0.5 mL in a 70-kg person). Moderate or greater effects were seen with doses of 2 mL or more with moderate clinical effects resulting from an average exposure of approximately 14 mg/kg. Major effects and fatalities were associated with doses of ≥10 mL, which in an 80-kg individual (the average weight of patients, when documented, was 83 kg) would correspond to a dose of 38 mg/kg.

In animals, pre- and post-marketing studies have demonstrated marked interspecies variability of toxic responses as well as differences in toxicity due to route of administration and dose [3]. Depending on route of administration, 10–30 mg/kg of tilmicosin

is a lethal IV or IM dose in a variety of species [3,6]. Death has been reported in humans at a dose of 5 mL (~21 mg/kg) [12].

In the Veenhuizen study, the volume of tilmicosin injected was unknown or not reported in 28% of cases. Where volume was known, the amount injected was reported as <0.5 mL in 67% of patients exposed by accidental injection; 3% reported exposure to between >0.5 and <1 mL; 1% to between 1 and <2.5 mL; 0.6% to between >2.5 mL and <4 mL; and 1% injected a volume of between 4 and 12 mL. The 2 accidental injection exposures that resulted in death had an estimated volume of injection of 10–12 mL. In 6 of the intentional exposure deaths, the volume of injection ranged from 3 mL to 60 mL. The volume of injection was unknown in the remainder [4].

In the case series of 36 accidental human tilmicosin exposures in Canada from March 1991 through August 1993, of the 12 patients with injection exposures who had electrocardiography performed, 1 was reported as having “peaked T waves” approximately 30 minutes after 1 mL injection into his arm. No other information is available for this patient. [5].

Management

Current management recommendations include healthcare facility referral for all parenteral exposures and a minimum of 8 hours observation with 24 hours of follow-up. In this study, toxicity with outcome codes of up to moderate severity, significant clinical findings, and prolonged effects were seen even with doses <0.5 mL, supporting previous recommendations [1] that all parenteral exposures should be referred to a healthcare facility.

LIMITATIONS

Because patient weight is not a mandatory field in the AAPCC database, determination of dose on a mg/kg basis was possible in only a small number of patients, limiting the precision of the dose-response relationship. Outcome codes reflect a number of different clinical effects, and specific effects were not coded with sufficient frequency for accurate dose-response correlation. Because of the nature of the AAPCC database, efficacy of various therapeutic interventions cannot be determined from this study.

CONCLUSIONS

Over 250 cases of human tilmicosin exposure are reported to poison centers per year and over 150 of those are parenteral. Most exposures produce no or minor effects, but fatalities have occurred with parenteral exposure. Doses in excess of 2 mL may produce moderate or greater effects and deaths may be seen with doses of 3 mL or greater. The case fatality rate in parenteral exposures is ten times the case fatality rate for all human exposures in the AAPCC database. Adverse and prolonged effects are reported at parenteral doses below 0.5 mL, suggesting that all parenteral exposures should be referred for healthcare facility evaluation.

The authors have no potential financial conflicts of interest to report.

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APPENDIX A: INCLUSION STATEMENT OF THE AMERICAN ASSOCIATION OF POISON CONTROL CENTERS

The American Association of Poison Control Centers (AAPCC; <http://www.aapcc.org>) maintains the national database of information logged by the country's 61 Poison Control Centers (PCCs). Case records in this database are from *self-reported* calls: They reflect only information provided when the public or healthcare professionals report an actual or potential exposure to a substance (e.g., an ingestion, an inhalation, a topical exposure, etc.), or request information/educational materials. Exposures do not necessarily represent a poisoning or overdose. The AAPCC is not able to completely verify the accuracy of every report made to member centers. Additional exposures may go unreported to PCCs and data referenced from the AAPCC should not be construed to represent the complete incidence of national exposures to any substance(s).

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APPENDIX B: AAPCC DATABASE OUTCOME CODES DEFINITIONS

- *No effect*: The patient developed no symptoms as a result of the exposure.
- *Minor*: The patient exhibited some symptoms as a result of the exposure, but they were minimally bothersome to the patient.
- *Moderate*: The patient exhibited symptoms as a result of the exposure that are more pronounced, more prolonged, or more of a systemic nature than minor symptoms.
- *Major*: The patient has exhibited symptoms as a result of the exposure that were life-threatening or resulted in significant residual disability or disfigurement.
- *Death*: The patient died as a result of the exposure or as a direct complication of the exposure, the complication being unlikely to have occurred had the toxic exposure not preceded the complication [15].