Re-evaluation of the regulation of omeprazole in racehorses: an evidence-based approach

Regulation of omeprazole in racehorses

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Abstract

Medication and doping control has been established in horseracing to ensure the integrity of the sport and the welfare of the horses. This ensures that horses do not compete under the influence of any drugs, including omeprazole, a therapeutic medication used to treat equine gastric ulcer syndrome. In this study, pharmacokinetic data were produced in equine plasma and urine following an oral administration of 4 mg/kg of generic buffered formulation of omeprazole to six Thoroughbred horses in five daily doses to determine an appropriate screening limit and detection time in equine plasma and to assess whether the current detection time of 72 hours in equine urine would be applicable when an alternative omeprazole product is administered. $C_{\text{max}}$ of 436 – 2432 ng/mL and $\text{AUC}_0-\tau$ of 1476 – 4371 ng.hr/mL were obtained for plasma and indicated, in conjunction with other published oral omeprazole studies, that an appropriate plasma screening limit would be 500 pg/mL with a detection time of 48 hours. Urine analysis showed that omeprazole could be detected for up to 25 hours above the previously established urine screening limit of 500 pg/mL, and thus, indicated that the detection time advice could be potentially reduced from 72 hours to 48 hours to allow more comprehensive treatment of gastric lesions.

Keywords

Omeprazole, pharmacokinetics, screening limit, detection time, medication control

Introduction

Equine Gastric Ulcer Syndrome (EGUS) refers to a spectrum of diseases, including hyperkeratotic, erosive and ulcerative lesions of the squamous mucosa and hyperaemic, erosive and ulcerative disease of the glandular mucosa, and affects many breeds of horse, including Thoroughbred racehorses. EGUS is now differentiated into Equine Squamous Gastric Disease
(ESGD) and Equine Glandular Gastric Disease (EGGD) according to the region of the stomach affected (Sykes, 2015a). The highest prevalence of ESGD occurs in Thoroughbred racehorses with 37% of untrained horses affected, increasing to 80–100% within 2–3 months of race training (Murray, 1996; Begg, 2003; Vatistas, 1999). EGGD is less well understood with reported prevalences of between 47% (Begg, 2003) and 65% (Sykes, 2015b) in Thoroughbred racehorses in Australia. Omeprazole is a proton pump inhibitor and its oral dosage is currently considered the treatment of choice for ESGD and EGGD.

Provision of high quality, evidence based information as to when to withdraw omeprazole and other medications in horses in training prior to a race day is a priority for horseracing regulators. A tenet of medication control in horseracing is that horses do not race under the pharmacological effects of drugs but are able to be treated with medication in training in the interests of their health and welfare. Medication control involves screening blood or urine samples to detect parent drug or metabolites and is not usually an issue of drug detection, but about determining the concentration at which a drug no longer has a significant pharmacological effect in a population of horses. With omeprazole, this is complicated by the range of doses used, oral formulation, high inter-individual variability (>30%) and by the mechanism of action of the drug.

Omeprazole is a prohibited substance according to the rules of the majority of racing jurisdictions with a wish to facilitate its use close to racing so that there is no recurrence of EGUS in susceptible horses whilst still not permitting racing under its direct effects. The European Horserace Scientific Liaison Committee (EHSLC) is a technical group representing European racing regulatory authorities who develop medication control advice in a harmonised way, based on Detection Times (DTs) and associated Screening Limits (SLs). The DT is an observed time point when the plasma or urine concentration falls below the respective SL following the last therapeutic dose. A DT of 72 hours was recommended by the EHSLC in
2006 for the control of omeprazole, based on a multiple administration study of GastroGard® paste (37% w/w) at a daily dose of 4 mg/kg for 28 days (Hannan, 2008).

In the last two years there has been a flurry of publications regarding the horse plasma PK of different omeprazole oral formulations. Given the large variability so reported for the plasma PK of the same formulation of omeprazole (GastroGard®) coupled with newer formulations of omeprazole licensed for use in the horse, the aim of this study was to assess the suitability of the current urine DT of 72 hours for omeprazole, its associated urine International Screening Limit (ISL) and to use the plasma data generated to propose an associated ISL for omeprazole in equine plasma.

**Materials and Methods**

**Chemicals and reagents**

Ammonium acetate was obtained from Sigma-Aldrich (UK) and methanol, ethyl acetate, sodium hydroxide, glacial acetic acid and hexane were from Fisher Scientific Ltd (UK). Water was purified using a Triple Red Duo Water system (Triple Red Laboratory Technology, UK).

Omeprazole was purchased as 1 mg/mL solution in methanol from Cerilliant and omeprazole-(5-methoxy-d₃) as powder from Sigma-Aldrich. A stock solution at a concentration of 1 mg/mL was prepared in methanol for omeprazole-d₃, and stored at −20 °C. Stock solutions were subsequently diluted with methanol in order to obtain separate spiking solutions at appropriate concentrations.
**Administration study**

Six Thoroughbred horses (1 filly and 5 geldings) with a mean ± SD weight of 523.2 ± 26.1 kg, aged from 4 to 9 years old, exercised in a manner consistent with that used in British training yards, fed a normal racehorse diet and housed at the British Horseracing Authority’s Centre for Racehorse Studies (Newmarket, UK) were used for this study. The study was ethically approved with the horses and personnel involved licensed under the UK’s Animals (Scientific Procedures) Act. A control blood and urine sample was taken from each horse on each of two days preceding dosing and again immediately before the first dose, via an intravenous catheter (Milacath®) placed into the left jugular vein of each horse on that first day of dosing. A dose of 4 mg/kg of UlcerGold® paste (37 % w/w, Zoetis) was administered orally in five daily doses at 9 am after a cereal-based racehorse mix had been given at 6 am. Hay was available ad lib. All the urine samples voided were collected following the first dose for 24 hours, immediately before each subsequent dose and following the final dose for up to 263 hours (12 days). Blood samples were collected immediately before each dose was administered and at 0.5, 1, 1.5, 2, 3, 4, 5, 6, 7, 9, 11, 13 and 15 hours following the first and the final dose, as well as, 23, 31, 47, 71, 95, 119, 143, 167, 215 and 263 hours following the final dose. Blood samples were collected in lithium heparin tubes and were centrifuged to separate plasma immediately after collection. Urine and plasma samples were stored at -20 °C prior to analysis.

**Sample analysis**

Plasma and urine samples were extracted and analysed using quantitative liquid chromatography tandem mass spectrometry (LC-MS/MS) methods which had been validated for omeprazole using measures of linearity, intra- and inter-batch precision and accuracy, specificity, selectivity and sensitivity (adhering to internal EHSLC quantitative method validation guidelines).
Plasma and urine detection methods were quantitatively validated in the ranges of 0.025 – 20 ng/mL and 0.1 – 20 ng/mL, respectively, and were shown to be linear with correlation coefficients greater than 0.99 when a weighting factor of 1/x was used. The methods for plasma and urine analysis were shown to be accurate and reproducible with low inter-batch variability for precision (within ± 7.0% for plasma and ± 6.2% for urine) and accuracy (within ± 3.6% for both plasma and urine) at all QC concentrations (0.025, 0.075, 10 and 17 ng/mL in plasma and 0.1, 0.25, 10 and 17 ng/mL in urine). QC samples diluted 1-in-100 also produced acceptable results (within ± 4.9% in plasma and ± 13.0% in urine).

During plasma extraction, each batch included a calibration line in duplicate at concentrations of 0.025, 0.05, 0.1, 0.5, 1, 5, 10 and 20 ng/mL and QC samples in duplicate at concentrations of 0.075, 10 and 17 ng/mL. 1 mL aliquots of plasma were spiked at a concentration of 100 ng/mL of omeprazole-d₃. Plasma proteins were precipitated by addition of 0.5 mL of acetonitrile and the sample was subsequently diluted with 7 mL of aqueous phosphate buffer (1 M, pH 6.8) and centrifuged at 3000 rpm for 15 minutes. Solid phase extraction (SPE) was performed using Varian Nexus (60 mg, 3 mL) cartridges, which were conditioned with 2 mL of methanol followed by 2 mL of water prior to sample loading. Cartridges were washed with 1 mL of water prior to eluting with 1 mL of methanol: acetonitrile (60:40, v:v).

During urine extraction, each batch included a calibration line in duplicate at concentrations of 0.1, 0.25, 0.5, 1, 2, 5, 10 and 20 ng/mL and QC samples in duplicate at concentrations of 0.25, 10 and 17 ng/mL. 1 mL aliquots of urine were spiked at a concentration of 100 ng/mL of omeprazole-d₃. Samples were diluted with 1 mL of aqueous ammonium acetate buffer (0.1 M, pH 9.0). SPE was performed using Varian Nexus (60 mg, 3 mL) cartridges, which were conditioned with 2 mL of methanol followed by 2 mL of water prior to sample loading. Cartridges were washed with 2 mL of hexane prior to eluting with 2 mL of methanol: ethyl
acetate (10:90, v:v). Liquid-liquid extraction (LLE) was performed by adding 1.5 mL of purified water.

Following the extraction, both urine and plasma extracts were dried at ambient temperature under oxygen-free nitrogen and subsequently reconstituted in 100 µL of methanol and 100 µL of aqueous ammonium acetate buffer (10 mM, pH 6.8). Extracts were transferred into glass LC vials and 5 µL was injected into the LC-MS/MS system.

Sample analysis was performed on a LC-MS/MS system consisting of a Waters Acquity I-Class UPLC interfaced with a Waters Xevo TQ-S triple quadrupole mass spectrometer operating in positive electrospray ionisation mode at a capillary voltage of 2.0 kV, a source temperature of 150 °C and a desolvation gas temperature at 550 °C. Collision gas was argon at a flow rate of 0.15 mL/min. Selected reaction monitoring (SRM) was performed for omeprazole using the precursor ion of m/z 346.0 and the product ions of m/z 198.1 (for quantification), m/z 151.0 and m/z 136.1 (for qualification) at cone voltage of 8 V and collision energy of 10, 30 and 32 eV, respectively. The SRM transition of m/z 349.0 to m/z 198.1 was used for omeprazole-d₃ (cone voltage of 8 V and collision energy of 10 eV).

Chromatographic separation was achieved on an Acquity HSS T3 (100 mm x 2.1 mm, 1.8 µm) reversed phase UPLC column using ammonium acetate in methanol (10 mM, pH 6.8) and aqueous ammonium acetate (10 mM, pH 6.8) as mobile phases. A gradient was operated at 60 °C and at a flow rate of 0.4 mL/min. It was started at 20 % organic for 0.5 minutes followed by an increase to 99.9 % organic at 5.5 minutes. This was held for 1 minute before resuming the initial conditions and re-equilibrating for 1.5 minutes. The total run time was 8.5 minutes.
Pharmacokinetic evaluation

Pharmacokinetic parameters were estimated using non-compartmental analysis with Phoenix WinNonlin 6.0 (Pharsight Corporation, Cary, NC). The area under the plasma curve for the first 24 hours post final dose (AUC$_{0\text{-}\text{tau}}$) was calculated using the log-linear trapezoidal rule. The estimated average concentration at steady-state (C$_{\text{avg}}$) was determined from the AUC$_{0\text{-}\text{tau}}$ divided by the dosing interval of 24 hours.

The methodology outlined by Toutain and Lassourd 2002 was used to estimate the effective plasma concentration (EPC), irrelevant plasma concentration (IPC), irrelevant urine concentration (IUC) and DT. The EPC was determined from the average steady-state plasma concentration (C$_{\text{avg,ss}}$) and estimated by dividing the AUC$_{0\text{-}24}$ for the last dose by the dosing interval (24 hours). The IPC creates the basis for the plasma SL, which is the concentration where the drug is no longer pharmacologically significant. The IPC was calculated by dividing the EPC by a safety factor of 500, to ensure there is no significant pharmacological effect for the majority of horses in a population.

Results

Pharmacokinetic analysis for orally administered omeprazole in plasma

Omeprazole was detected in the post-administration plasma samples from all six horses (Figure 1). Maximum concentrations (C$_{\text{max}}$) were measured between 436 and 3304 ng/mL between 0.5 and 4 hours (t$_{\text{max}}$) following either the first or final dose (Table 1). There was very little accumulation of omeprazole in plasma as shown by the trough levels, from the first dose through to dose four.
The terminal half-life (t_{1/2}) ranges from 6 to 18 hours and the AUC_{0-tau} ranges from 1476 to 4371 ng.hr/mL. The estimated mean and standard deviation for C_{avg,ss} omeprazole concentration was 120 ± 46 ng/mL, which can be considered as the effective plasma concentration (EPC) for the 4 mg/kg once a day oral regimen in Thoroughbred horses. Different safety factors were applied to the EPC value to establish the appropriate irrelevant plasma concentration (IPC) (Table 2). Using a safety factor of 500 the estimated IPC is 240 pg/mL with a corresponding DT of 47 hours.

**Pharmacokinetic analysis for orally administered omeprazole in urine**

Omeprazole was detected in the post-administration samples from all six horses (Figure 2). The C_{max} of omeprazole varied between 55 and 504 ng/mL and were observed between 2 and 11 hours either following the first or final dose administered (Table 3). The ISL of 500 pg/ml for omeprazole in urine was exceeded for up to 25 hours following the final dose, whilst detection was still possible at significantly lower concentrations for up to 71 hours post-administration.

**Discussion**

Omeprazole is a therapeutic drug which attracts debate with regards to its use in horseracing. In two studies which investigated omeprazole’s effect on performance markers in healthy horses, no statistically significant improvement (Kollias-Baker, 2001; McKeever, 2006). However, it has been shown to improve racing performance in the sense of returning a horse to a normal condition (Johnson, 2001). It therefore remains a therapeutic but prohibited substance on raceday and is controlled via an ISL in urine with related DT advice in most racing jurisdictions.
This study set out to provide data to re-evaluate existing international regulatory omeprazole DT advice, the existing ISL in urine and to support a new ISL in plasma. An IPC can be used as the basis to propose a new plasma SL. For the purposes of determining an IPC for an oral therapy, Toutain and Lassourd 2002 recommend using pharmacokinetic data from an intravenous study at the therapeutic oral dose. The only published intravenous studies for omeprazole in horse with resulting pharmacokinetic parameters are those by Sykes et al. 2015d and Jenkins et al. 1992. Both intravenous administration studies were at 0.5 mg/kg, and not the 4 mg/kg used orally in this case, and the clearance values determined for a single dose were 12.9 (Sykes et al. 2015d) and 14.7 (Jenkins et al. 1992) mL/min/kg. The estimated IPC from these intravenous studies are 430 (Sykes et al. 2015d) and 379 (Jenkins et al. 1992) pg/mL using a safety factor of 500 for a dose of 4 mg/kg. These values are higher but similar to the IPC determined from the oral pharmacokinetics determined in the herein study (240 pg/mL).

Recent oral pharmacokinetic studies involving omeprazole carried out for the purposes of bioequivalence investigation have not had sufficient analytical sensitivity for the purposes of DT advice. They have shown that the PK of omeprazole in plasma is not significantly altered following the administration of different formulations (enteric coated granules versus buffering with an alkaline medium) when compared with GastroGard® (buffered) (Birkmann et al. 2014; Sykes et al. 2015c). Computed area under the curve (AUC$_{0-\infty}$) for the Sykes et al. 2015c study was shown to be approximately 417 – 2083 ng.hr/mL following a single 4 mg/kg dose of GastroGard® to 12 Thoroughbred horses. In another PK study following oral multi-dose administration of 4 mg/kg per day of a new gastro-resistant omeprazole formulation to horses the AUC$_{0-\infty}$ was 1382±861 ng.hr/mL on day 1 slightly reducing to 831±387 ng.hr/mL on day 29 (DiSalvo et al. 2016). One study that was carried out for the purposes of determining a DT in horseracing showed no significant change in AUC$_{0-\text{tau}}$ despite four daily oral doses of 3.7 – 5.2 mg/kg of GastroGard® to nine Thoroughbred horses (Knych, 2017). These
pharmacokinetic parameters obtained by Knych et al. included an average AUC\textsubscript{0-\text{tau}} of 305 ± 141 ng.hr/mL and an average steady-state serum concentration (C\textsubscript{avg}) of 12.7 ± 5.89 ng/mL which are considerably different to those obtained by the other studies.

Although direct extrapolations between formulation across studies is not possible due to high inter-individual variability between animals, the small number of horses used in different studies and different analytical methods, any indirect extrapolations should be made with caution, the plasma exposure, as determined by both C\textsubscript{max} and AUC, in this herein oral UlcerGold® administration at 4 mg/kg per day is consistent with the Birkmann et al. 2014; Sykes et al. 2015c and DiSalvo et al. 2016 studies which were also carried out at the same dose. However, a much higher plasma exposure (~10 times) was observed in these studies compared with the omeprazole serum exposure by Knych et al. 2017 at the same dose.

Since SLs are calculated from drug exposure measurements at the therapeutic dose, the discrepancy between the study by Knych et al. 2017 and the other studies may make it difficult to harmonise SLs across racing jurisdictions. The only major difference between the Knych et al. 2017 study and the other studies is that serum concentrations were analysed for the former and plasma for the latter. The study by Knych et al. 2017 used serum separator tubes; one explanation for the apparent lower exposure may be that omeprazole diffused into the separating gel, causing a reduction in the measured serum drug concentration. Alternatively, serum concentration for omeprazole may be lower than the corresponding plasma concentration due to lower omeprazole binding to serum as part of the clotting process. Omeprazole is known to have high plasma protein binding, however, a lower binding affinity to serum proteins will lead to a lower omeprazole serum concentration. In this case a lower SL would be required for serum; however, further examination of the serum data suggests that the DT will be similar to the plasma studies based upon an irrelevant serum concentration.
One way forward with regard to generating an ISL in plasma for the oral administration of omeprazole is to use the IPC calculated from the published intravenous studies. In fact, Toutain and Lassourd 2002 recommend using intravenous data for the determination of the IPC, however, for omeprazole the intravenous studies are at a dose eight times smaller than that for the herein oral study. Assuming dose linear pharmacokinetics between 0.5-4 mg/kg then the IPC determined from the intravenous studies would encompass all oral formulations of omeprazole as it would represent the maximum exposure resulting from an oral administration (i.e. bioavailability = 100%).

Plasma data from the herein UlcerGold® study shows that omeprazole can be detected for up to 287 hours post-administration above the LLOQ of the 25 pg/mL of the method following an oral administration of 4 mg/kg per day. However, the DT of 47 hours was determined using an IPC of 240 pg/mL. Previously, omeprazole has been detected in plasma for up to 24 hours post-administration when 4 mg/kg of GastroGard® (37 % w/w) was orally administered for 28 days (Hannan, 2008). This shorter detection time was due to lower method sensitivity (LLOQ of 1 ng/mL). The results from these two studies are consistent as omeprazole was detected for up to 23 hours post-administration above the concentration of 1 ng/mL in the herein study.

A DT of 47 hours in plasma using an IPC of 240 pg/mL and 25 hours in urine using the ISL of 500 pg/mL was calculated for omeprazole based on six horses in this study. However, if a plasma screening limit of 500 pg/mL was applied, based upon the IPC determined from intravenous clearance, then the DT would be 31 hours. Interestingly, an IUC of 500 pg/mL can be estimated from this study by multiplying a plasma SL of 500 pg/mL by the urine to plasma steady-state omeprazole concentration ratio (Rss=1) which is in fact equal to (and therefore supports) the current urine ISL of 500 pg/mL for omeprazole.
Tellez et al. 2005 have shown that a single oral 4 mg/kg dose of omeprazole (GastroGard®) increases stomach contents pH above a control group for up to 24 hours. Furthermore, Merritt et al. 2003 have shown that 4 mg/kg per day oral dose GastroGard® for 7 days statistically increases intragastric pH for up to 14 hours relative to pre-administration on days 1 and 7. Daurio et al. 1999 showed a more pronounced effect using an oral paste formulation of omeprazole at 4 mg/kg which inhibited both basal and pentagastrin-stimulated gastric acid secretion by 99% at 5-8 h after treatment and by 83% (basal) and 90% (pentagastrin-stimulated) at 21-24 hours. Sykes et al. 2017 have shown that dose and diet affect the response to omeprazole in the horse in an inconsistent manner. Clearly, there are several factors that influence the duration of effect of omeprazole which is not surprising given the fact it is a quasi-irreversible inhibitor of H⁺, K⁺-ATPase. A DT of 48 hours for oral omeprazole allows for both the herein suggested plasma and urine SLs as well as the duration of action observed in clinical equine studies.

DTs are used by the treating veterinarian to recommend a withdrawal time (WT) for the drug before racing. WTs are longer than DTs as they include variability such as age, health and the particular drug product administered (Toutain, 2010). To extrapolate a WT experimentally, it is recommended to use an uncertainty factor determined from a Monte Carlo simulation which ensures that the 90th percentile of the population will not have a positive result. This simulation combines sources of variability simultaneously to generate an example population of DTs without completing a large population survey. The proposed DT of 48 hours should therefore be converted using an uncertainty factor of 1.4 as outlined by Toutain 2010, to give a WT of 72 hours.

Orally administered omeprazole is an effective treatment for ESGD which can be debilitating, particularly in horses on which additional demands of competition are placed. In a study by Johnson et al. 2001, 403 horses treated for ESGD with omeprazole for 28 days at 4 mg/kg...
bodyweight per day showed 94% improvement, with 63% completely healed. This was reflected in a recent trial with 60 horses treated for ESGD, in which 88% showed improvement and 75% completely healed but in which the traditional 4 mg/kg per day dose was not the most effective; horses treated with 1 or 2 mg/kg per day showed 100% improvement and 89% healed, and 100% improvement and 94% healed respectively (Sykes, 2015b). The reported response rates for EGGD for oral omeprazole monotherapy are lower, with overall results at different doses (1, 2 and 4 mg/kg) showing 34% improvement and 14% complete healing (Sykes, 2015b). It is therefore desirable that as far as possible within the principle of racing without the benefit of drugs, horses that need to be treated with omeprazole are treated in the confidence that they will neither risk a post-race adverse analytical finding (‘positive’) nor have their health compromised. The new data reported herein for orally administered, in conjunction with other published studies, suggest that a plasma SL of 500 pg/mL should be used in addition to the existing urine ISL of the same concentration. A detection time of 48 hours is recommended which should assist those balancing what is best for an individual horse with what is needed to protect the integrity of the sport in which they are involved.

Conflicts of interest

The authors have no commercial conflicts of interest; however the authors are either employed or consulting to a regulatory agency.

References


doses to exercised Thoroughbred horses. Journal of Veterinary Pharmacology and Therapeutics, 40, 92-96.


Authors’ Contribution Statement

MV – one of main authors, analytical method development, validation and sample analysis

LH – one of main authors, veterinary input for drug administrations

PH – project management and manuscript editing

CP – project management and manuscript editing

SP – pharmacokinetics

All the authors have read and approved the final manuscript.
Table 1  Summary of plasma pharmacokinetic parameters for omeprazole following administration of 4 mg/kg once a day for five doses of UlcerGold® to six exercised Thoroughbred horses.

<table>
<thead>
<tr>
<th></th>
<th>Horse 1</th>
<th>Horse 2</th>
<th>Horse 3</th>
<th>Horse 4</th>
<th>Horse 5</th>
<th>Horse 6</th>
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<tbody>
<tr>
<td>$C_{\text{max}}$ (ng/mL)</td>
<td>2432</td>
<td>1242</td>
<td>435.8</td>
<td>1596</td>
<td>1329</td>
<td>1012</td>
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<tr>
<td>$t_{\text{max}}$ (h)</td>
<td>3.1</td>
<td>4.0</td>
<td>4.0</td>
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<td>0.5</td>
<td>1.0</td>
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<td>$t_{1/2}$ (h)</td>
<td>11</td>
<td>9.1</td>
<td>16</td>
<td>18</td>
<td>18</td>
<td>6.1</td>
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<tr>
<td>$\text{AUC}_{0-\text{tau}}$ (ng.hr/mL)</td>
<td>3625</td>
<td>4371</td>
<td>1476</td>
<td>2946</td>
<td>3139</td>
<td>1751</td>
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<tr>
<td>$C_{\text{avg}}$ (ng/mL)</td>
<td>151</td>
<td>182</td>
<td>62</td>
<td>123</td>
<td>131</td>
<td>73</td>
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Table 2  Safety Factors relative to an EPC of 120 ng/mL and corresponding Detection Times

<table>
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<tr>
<th>Safety Factor</th>
<th>Irrelevant Plasma Concentration (ng/mL)</th>
<th>Detection Time (hrs)</th>
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<tr>
<td>10</td>
<td>12</td>
<td>15</td>
</tr>
<tr>
<td>50</td>
<td>2.4</td>
<td>23</td>
</tr>
<tr>
<td>100</td>
<td>1.2</td>
<td>23</td>
</tr>
<tr>
<td>500</td>
<td>0.24</td>
<td>47</td>
</tr>
<tr>
<td>1000</td>
<td>0.12</td>
<td>71</td>
</tr>
</tbody>
</table>
Table 3  Summary of urine pharmacokinetic parameters for omeprazole following administration of 4 mg/kg once a day for five doses UlcerGold® to six exercised Thoroughbred horses

<table>
<thead>
<tr>
<th></th>
<th>Horse 1</th>
<th>Horse 2</th>
<th>Horse 3</th>
<th>Horse 4</th>
<th>Horse 5</th>
<th>Horse 6</th>
</tr>
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<tbody>
<tr>
<td>$C_{\text{max}}$ (ng/mL)</td>
<td>216.8</td>
<td>85.6</td>
<td>54.8</td>
<td>504.2</td>
<td>312.2</td>
<td>87.1</td>
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<tr>
<td>$T_{\text{max}}$ (h)</td>
<td>5.3</td>
<td>11.1</td>
<td>3.5</td>
<td>1.8</td>
<td>1.9</td>
<td>2.1</td>
</tr>
<tr>
<td>Detection time (h)*</td>
<td>9.6</td>
<td>12.8</td>
<td>12.8</td>
<td>24.7</td>
<td>8.3</td>
<td>10.5</td>
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<tr>
<td>Overall Time detected (h)**</td>
<td>28.2</td>
<td>26.6</td>
<td>29.9</td>
<td>47.3</td>
<td>25.7</td>
<td>70.9</td>
</tr>
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</table>

*Above the SL of 500 pg/mL  
**Above LOD of the method
Figure 1

Figure 2