Feasibility of Using Half-Life Multipliers To Estimate Extended Withdrawal Intervals following the Extralabel Use of Drugs in Food-Producing Animals

R. GEHRING,1* R. E. BAYNES,1 A. L. CRAIGMILL,2 AND J. E. RIVIERE1

1Center for Chemical Toxicology Research and Pharmacokinetics, Food Animal Residue Databank, College of Veterinary Medicine, North Carolina State University, Raleigh, North Carolina 27606; and 2Environmental Toxicology Extension, Food Animal Residue Avoidance Databank, Department of Environmental Toxicology, University of California at Davis, Davis, California 95616, USA

MS 03-205: Received 12 May 2003/Accepted 9 October 2003

ABSTRACT

Under the Animal Medicinal Drug Use Clarification Act of 1994, veterinarians are legally allowed to use drugs in food-producing animals in an extralabel manner. This could potentially lead to violative residues in food of animal origin. It is therefore essential that an appropriately extended withdrawal interval be established. Ideally, these extended withdrawal intervals should be calculated on the basis of the tissue half-life of the drug in the target animal. However, these data are not readily available for all drugs of extralabel use in food-producing animals. For this reason, the use of a half-life multiplier has been proposed as a simple alternative method to estimate the effective tissue half-life of a drug. Extended withdrawal intervals, estimated using various half-life multipliers, were compared with the withdrawal intervals calculated using actual tissue half-lives. For the group of drugs investigated, a half-life multiplier of 5 resulted in estimates of extended withdrawal intervals that were potentially inadequate to prevent violative tissue residues for drugs that had relatively long tissue half-lives, high tolerances, or both. This is possibly because fewer half-lives are required for these drugs to reach the target tissue concentrations following administration at label doses. Use of a smaller half-life multiplier (in this case 3) is therefore suggested to ensure that extended withdrawal intervals are adequate to prevent violative tissue residues.

Veterinary pharmaceuticals approved for use in food-producing animals have withdrawal periods that indicate how soon after dosing the edible products from the animal can be used for human consumption (8). The withdrawal period must provide enough time for the drug and its metabolite(s) to deplete to target concentrations that are below limits that have been established as safe by the appropriate regulatory authority (5,6). In the United States, the Center for Veterinary Medicine of the Food and Drug Administration (FDA-CVM) refers to these target concentrations as tolerances. The withdrawal time that appears on the label of a product is established by the FDA-CVM with data from residue studies conducted in a particular species to which the highest dose indicated in the instructions on the label has been administered (8). The withdrawal period is based on the tissue that takes the longest to reach target concentrations because of a slow rate of depletion or a low tolerance (8). This tissue is referred to as the target tissue. The FDA-CVM sets withdrawal times by linear regression through the drug concentration versus time points on a semi-logarithmic scale. The withdrawal time is then the point at which it can be predicted with 95% statistical confidence that residue concentrations in the target tissue of 99% of the animals have decreased to concentrations that are below the established tolerance (4,8). This approach is based on the assumption that, on a semi-logarithmic scale, drug concentrations decrease in a linear manner with passing time. Independence and normality of residual distribution on a log scale and equality of variances at each sampling point are also assumed. The merits and limitations of these assumptions have been discussed by other authors (1–4).

For a particular target concentration, the withdrawal time is a function of the initial concentration of the drug in the edible tissues and the rate at which the drug and its active metabolites are eliminated from those tissues (Fig. 1). The initial concentration is dependent on the administered dose, drug formulation, and route of administration. The rate of elimination can vary with formulation, route of administration, species, dose, and various pathophysiological conditions (4–6). Administration of a higher dose or any changes that result in a slower rate of depletion of the residues would require that an appropriate extended withdrawal interval be established to prevent violative residues in the tissues of the treated animal (4–6). Deviation from the instructions that appear on the label of a drug (extralabel use) can lead to changes in a number of these factors. Under the Animal Medicinal Drug Use Clarification Act of 1994, veterinarians are legally allowed to use drugs in food-producing animals in an extralabel manner, provided that an appropriately extended withdrawal time is established (4).

For clarity, the term withdrawal time (WDT) will be used in this article to refer to the withdrawal period indicated on the label of the product, whereas the extended withdrawal period following extralabel use will be referred to as the withdrawal interval (WDI).

* Author for correspondence. Tel: 919-513-6803; Fax: 919-513-6358; E-mail: ronette.gehring@ncsu.edu.
The administration of a higher dose to the same species and for the same indications that appear on the label would lead to a higher initial concentration of the drug or its metabolite(s) in the tissues, but an unchanged rate of depletion (assuming linear, first-order, nonsaturable pharmacokinetics). A measure of the rate of depletion is the elimination half-life, which is defined as the time it takes for the amount of drug in the tissue to decrease to 50% of the original concentration (5). The elimination half-life is calculated by determining the slope of the terminal portion of the semilogarithmic plot of drug concentration time points and converting this to a half-life by equation 1.

$$\text{Half-life} = \frac{-0.693}{\text{slope}} \quad (1)$$

where $0.693 = \ln(2)$. 

Assuming that the half-life does not change with different doses, which is probably the case for most drugs administered at therapeutic levels, and on the basis of the definition of the elimination half-life, the withdrawal period would need to be increased by one half-life if the dose indicated on the label were doubled because this would be the time required for the concentration of the residue to deplete to the same concentration as it would be following administration at the label dose (5). A rational extended WDI following administration of doses higher than that which appears on the label can therefore be estimated by adding one tissue elimination half-life to the WDT for each doubling of the dose (4).

An accurate estimate of the tissue elimination half-life is required to predict an extended WDI. Ideally the elimination half-life should be calculated from the experimental data generated from the residue studies used to calculate the label WDT because these will reflect the actual tissue half-life of that particular formulation in the target animal. However, the results of these residue studies are not routinely published in the scientific literature, and these data are not readily accessible for all marketed products.

An alternative approach is to estimate the elimination half-life on the basis of the label WDT, which reflects the number of tissue elimination half-lives required for the concentration of the residue to reach tolerance levels (5). The number of half-lives required for the tissue residues of a drug to reach target concentrations is dependent on the value of the tolerance, with more half-lives required for drugs with lower tolerances thus requiring a greater amount of the drug to be excercited before the tissue is fit for human consumption. On the basis of the definition of a half-life, 88% of the drug residue will have been eliminated from the body after 3 tissue half-lives, 97% after 5 tissue half-lives, and 99.9% after 10 tissue half-lives (5). Because the number of tissue elimination half-lives contained within the WDT of a drug is unknown, it must be estimated. A common practice among veterinary practitioners is to assume that, for the majority of drugs, five half-lives are required for tissue concentrations to be depleted to below tolerance levels (i.e., 97% of the residue is eliminated from the tissue).

In this article, the estimate of the number of half-lives contained within the WDT is referred to as the half-life multiplier (HLM). It should be pointed out that the fewer the number of half-lives assumed to be contained within the WDT (i.e., the smaller the HLM), the longer the estimated tissue half-life. Because the extended WDI is estimated by adding a multiple of the tissue elimination half-life to the WDT, a smaller HLM will result in a more conservative estimate. Ideally, the estimated WDI should be adequate to ensure that there are no violative drug residues in the edible tissue, without being too conservative and re-
TABLE 2. Target concentrations and half-lives for marker residues of selected drugs in target tissues

<table>
<thead>
<tr>
<th>Drug</th>
<th>Marker residue</th>
<th>Target tissue</th>
<th>Tolerance (ppm)</th>
<th>Actual tissue half-life (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spectinomycin</td>
<td>Parent spectinomycin</td>
<td>Kidney</td>
<td>0.1</td>
<td>72</td>
</tr>
<tr>
<td>Oxytetracycline</td>
<td>Sum of residues of the tetracyclines</td>
<td>Kidney</td>
<td>12</td>
<td>29</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Liver</td>
<td>6</td>
<td>29</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Muscle</td>
<td>2</td>
<td>37</td>
</tr>
<tr>
<td>Danofloxacin</td>
<td>Parent danofloxacin</td>
<td>Liver</td>
<td>0.2</td>
<td>10</td>
</tr>
<tr>
<td>Tilmicosin</td>
<td>Parent tilmicosin</td>
<td>Liver</td>
<td>1.2</td>
<td>204</td>
</tr>
<tr>
<td>Florfenicol</td>
<td>Florfenicol amine</td>
<td>Liver</td>
<td>3.7</td>
<td>257</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>Erythromycin</td>
<td>Uncooked edible tissues</td>
<td>0.1</td>
<td>10</td>
</tr>
</tbody>
</table>

* Extracted from Freedom of Information documents.

* Calculated from data from tissue residue studies summarized in Freedom of Information documents.

resulting in economic loss to the producer. The purpose of this study was to determine the optimal value of the HLM for certain drugs by comparing WDIs calculated with tissue half-lives that were estimated using various HLMs with the WDI for each drug that was calculated using the actual tissue half-life.

**MATERIALS AND METHODS**

Extended WDIs were calculated for selected drugs using actual tissue half-lives, and estimated tissue half-lives were determined using various HLMs. The WDIs calculated for each drug with the use of these different methods were compared on the basis of a single, arbitrary, extralabel dose of double the label dose.

**Selection of drugs.** Antimicrobials approved in the United States for parenteral administration to cattle, for which a summary of the residue study submitted for approval to the FDA was available in the Freedom of Information summaries on the FDA-CVM Web site, were selected (7, 9–12). A summary of the selected drugs with tolerances for their marker residues in the appropriate target tissue is given in Table 2.

**Calculation of tissue half-lives.** Average residue concentrations measured in the target tissue at time points during the residue study were obtained from the Freedom of Information summaries. These points were plotted on a semi-logarithmic scale, and the slope of the depletion curve was determined by linear regression. This slope was used to calculate the actual tissue half-life (ATH) in equation 1.

**Estimation of tissue half-lives by the HLM approach.** Estimated tissue half-lives (ETH) were calculated with HLMs of 3, 4, and 5 (equation 2), thus reflecting scenarios for which 88, 94, and 97%, respectively, of the drug residue must be eliminated for tolerance levels to be reached.

\[ \text{ETH} = \frac{\text{WDT}}{\text{HLM}} \]  

**Calculation of extended WDIs.** Assuming that double the label dose was administered to the animal, extended WDIs were calculated by (i) the WDI1 method by adding the ATH that was calculated from the experimental data to the label WDT (equation 3); (ii) the WDI2 method by adding the tissue half-lives that were estimated with a HLM of 3, 4, or 5 (ETH) to the label WDT (equation 4); and (iii) the WDI3 method by adding a safety factor (SF) of 5 or 10% of the label WDT to WDI2 (equation 5).

\[ \text{WDI1} = \text{WDT} + \text{ATH} \]  
\[ \text{WDI2} = \text{WDT} + \text{ETH} \]  
\[ \text{WDI3} = \text{WDT} + (\text{SF} \times \text{WDT}) \]

The first approach resulted in only a single WDI, whereas the second and third techniques resulted in three and two different WDIs, respectively. All calculated WDIs were rounded up to the next day.

**RESULTS**

The tissue half-lives estimated from the label WDTs are listed in Table 1, and the actual target tissue half-lives, calculated from experimental data by the method described above, are listed in Table 2. The WDIs calculated using...
FIGURE 3. Comparison of extended withdrawal intervals (days) calculated using the two different estimates of the tissue elimination half-life.

FIGURE 4. Comparison of extended withdrawal periods calculated using a half-life multiplier (HLM) of 5 with different safety factors and using actual tissue half-lives.

For all drugs except tilimicosin and florfenicol, the WDIs calculated with a HLM of 5 were equal to or greater than the WDIs calculated using actual tissue half-life. WDIs determined with HLMs of 3 and 4 were more conservative, with the HLM of 3 resulting in adequate WDIs for tilimicosin and florfenicol. The results of adding various safety factors are summarized in Figure 4.

Figure 3 is a radar chart that compares the WDIs calculated using half-lives estimated with a HLM of 5 with the WDIs calculated using actual target tissue half-lives and also illustrates trends in the relationship between these two WDIs and the relative length of the WDI. The concentric lines around the center of the radar plot represent increasing length of WDI in increments of 10 days. The length of the WDIs for each drug is indicated by a point on the radar plot placed at the appropriate distance from the center. For spectinomycin, erythromycin, and danofloxacin, which have relatively short WDIs, the points are superimposed, indicating that they are equal. For florfenicol and tilimicosin, which have relatively long WDIs, the points representing the WDIs calculated with a HLM of 5 are closer to the center, and therefore shorter than the WDIs calculated using actual tissue half-lives. This, however, is not the case for oxytetracycline. It would therefore seem that, except for oxytetracycline, extended WDIs calculated with a HLM of 5 are inadequate for the drugs with longer label WDIs and hence relative WDIs.

Similarly, Figure 5 compares the WDIs calculated with a HLM of 5 and adding a safety factor of 10% with the WDIs calculated using actual tissue half-lives. In this figure, all points for WDIs calculated with a HLM of 5 and a safety factor of 10% lie further from the center of the chart than the points for the WDIs calculated using actual tissue half-lives. Addition of a safety factor of 10% therefore ensured that, for those drugs with longer WDIs, the WDIs calculated with a HLM of 5 were at least as long as the WDIs calculated with the actual tissue half-lives.

DISCUSSION

For the set of drugs investigated, assuming that tissue half-lives are reflected in the label withdrawal time, extended WDIs resulted in estimates that were inadequate for some of the drugs (when compared to the WDIs calculated using the actual tissue half-lives). Similar WDIs...
were obtained with a HLM of 5 and the actual tissue half-lives for those drugs with relatively short label WDTs and low tolerances (danofloxacin, spectinomycin, and erythromycin) (Fig. 3 and Table 2). The low tolerances for these three drugs (0.2, 0.1, and 0.1 ppm, respectively) make it likely that at least 97% of the drug must be eliminated for target tissue concentrations to be reached. This means that the label WDTs for these drugs are likely to be at least five tissue half-lives long, but still relatively short because of the rapid decline of target tissue concentrations (half-lives of 10, 72, and 10 h, respectively). In contrast, for tilmicosin and florfenicol, the WDTs calculated with a HLM of 5 were shorter than the WDTs calculated using the actual tissue half-lives. Both tilmicosin and florfenicol have relatively long half-lives (204 and 257 h, respectively) and high tolerances (1.2 and 3.7 ppm, respectively). It is therefore likely that, despite the long label WDTs, which can be attributed to the long tissue half-lives, fewer than five tissue half-lives are required for the concentrations of the residues of these two drugs to reach target concentrations when administered according to label instructions. This would be because less than 97% of the residue needs to be excreted for the high target concentrations to be reached.

For oxytetracycline, all HLMs resulted in WDTs that were more conservative than if the actual tissue half-life was used. Oxytetracycline has a relatively short inherent tissue half-life but a long label WDT because of its long-acting formulation. A slow, sustained, and perhaps erratic release from the long-acting formulation might have made it necessary for the label WDT to be increased beyond the period of five half-lives to prevent possible violative residues.

The results of this study indicate that using a HLM to estimate the elimination half-life of a drug is potentially feasible in the absence of readily available experimental data to calculate the tissue elimination half-life of a drug. It is also superior to the use of pharmacokinetic data from literature sources, which represent mean values (50th percentile) of the population rather than the 99th percentile half-lives calculated from regulatory WDTs using a HLM. Also, the use of half-lives from literature sources does not guarantee that the half-life associated with the rate-limiting (target) tissue has been selected. The HLM approach, which bases the estimate of the half-life on the label WDT, obviates this problem.

However, extended WDTs calculated with a HLM of 5 might be inadequate to ensure that there are no violative tissue residues following the extralabel use of some drugs in food-producing animals, and a HLM of 3 should be considered if a more conservative estimate is required. Alternatively, a safety factor of 10% of the label WDT should be added to the WDI if it is calculated with a HLM of 5. However, the addition of a safety factor is arbitrary and hence less desirable, whereas a HLM of 3 reflects the small number of half-lives required for some of the drugs to reach target concentrations. Further investigation with a larger group of drugs is needed to confirm this observation.

ACKNOWLEDGMENT

This work was supported by the USDA Cooperative State Research, Education, and Extension Service.

REFERENCES