ORIGINAL RESEARCH PEER REVIEWED

Homogeneity and stability in drinking water of oral nonsteroidal anti-inflammatory drugs labelled for swine in Europe

Irene Mayós, PhD; Jaume Bosch, DVM; Emili Fadurdo, BS; Josep Homedes, DVM, PhD

Summary

Objectives: To verify the stability and homogeneity in drinking water of five nonsteroidal anti-inflammatory drugs (NSAIDs) labeled for pigs in Europe, including oral solutions of ketoprofen (300 mg per mL) and paracetamol (200 mg per mL) and soluble powders of sodium salicylate 100%, paracetamol (200 mg per g), and acetylsalicylic acid 100%, under field conditions.

Materials and methods: A solution of each product was prepared according to label instructions in a 300-L farm tank, without stirring. Active ingredient concentrations were determined by high-performance liquid chromatography on three samples collected at three standard depths in the tank (high, medium, and low) at 5 minutes, 12 hours, and 24 hours post mixing.

Results: No time-related statistically significant differences were observed in active-principle concentrations. However, significant differences were detected at different sampling depths for sodium salicylate and paracetamol powder and solution. Some variability was observed for acetylsalicylic acid, but differences were not statistically significant. Concentrations obtained at all time points and sampling depths for ketoprofen approached calculated values, indicating better homogeneity and stability in drinking water.

Implications: When NSAIDs in drinking-water tanks are used to treat farm animals, variability in dose may occur if the water is not adequately stirred after product addition. Lack of homogeneity may produce overdose or underdose, thereby increasing the risk of adverse events and violative residues in the carcasses or the possibility of lack of efficacy, respectively. This situation is more evident when the added product is a soluble powder rather than a solution.

Keywords: swine, ketoprofen, paracetamol, salicylic acid, drinking water treatment

Received: January 12, 2012
Accepted: May 29. 2012

Resumen - Homogeneidad y estabilidad de medicamentos antiinflamatorios no esteroidales orales en el agua de bebida autorizados para cerdos en Europa

Objetivos: Verificar, bajo condiciones de campo, la estabilidad y homogeneidad en el agua de bebida de cinco medicamentos antiinflamatorios no esteroidales (NSAIDs por sus siglas en inglés) autorizados para cerdos en Europa, incluyendo soluciones orales de ketoprofen (300 mg por mL) y paracetamol (200 mg por mL) y polvo soluble de silicato de sodio 100%, paracetamol (200 mg por g), y ácido acetilsalicílico 100%.

Materiales y métodos: En un tanque de granja de 300 L, se preparó sin agitar una solución de cada producto de acuerdo a las instrucciones de la etiqueta. Se determinó la concentración de ingrediente activo a través de la cromatografía líquida de alta resolución en tres muestras recolectadas a tres profundidades estándares (alta, media, y baja) en el tanque a los 5 minutos, 12 horas, y 24 horas post mezcla.

Resultados: No se observaron diferencias estadísticamente significativas en las concentraciones de principio activo con relación al tiempo de muestreo. Sin embargo, se detectaron diferencias significativas a diferentes profundidades en las muestras de solución y polvo de paracetamol y silicato de sodio. Se observó variabilidad para el ácido acetilsalicílico, pero las diferencias no fueron estadísticamente significativas. Las concentraciones obtenidas en todos los tiempos y profundidades para ketoprofen se aproximaron a los valores calculados, indicando una mejor homogeneidad y estabilidad en el agua de bebida.

Implicaciones: Cuando los NSAIDs se utilizan para tratar animales de granja en los tanques de agua de bebida puede haber variabilidad en la dosis si el agua no se agita adecuadamente después de la adición del producto. La falta de homogeneidad puede producir una sobredosis o una dosis inferior, incrementando así el riesgo de reacciones adversas y la presencia de residuos no permitidos en la canal o la posibilidad de falta de eficacia, respectivamente. Esta situación es más evidente cuando el producto se agrega como polvo soluble y no en solución.

Résumé - Homogénéité et stabilité dans l'eau de boisson de médicaments anti-inflammatoires non-stéroïdiens homologués pour les porcs en Europe

Objectifs: Vérifier, dans des conditions de champs, la stabilité et l'homogénéité dans l'eau de boisson de cinq médicaments anti-inflammatoires non-stéroïdiens (AINS) homologués pour les porcs en Europe,

IM, JH: Esteve Veterinaria, Laboratorios Dr Esteve SA, Barcelona, Spain.

JB: Clinobs SL (Estudis Clínics Veterinaris), Banyoles (Girona), Spain.

EF: Laboratorio de Diagnóstico General, Barcelona, Spain.

Corresponding author: Dr Josep Homedes, Esteve Veterinaria, Laboratorios Dr Esteve SA, Avda Mare de Déu de Montserrat, 221, 08041 Barcelona, Spain; Tel: + 34 93 4466318; Fax: + 34 93 446 6201: E-mail: jhomedes@esteve.es.

This article is available online at http://www.aasv.org/shap.html.

Mayós I, Bosch J, Fadurdo E, et al. Homogeneity and stability in drinking water of oral nonsteroidal anti-inflammatory drugs labelled for swine in Europe. *J Swine Health Prod.* 2012;20(6):270–275.

incluant des solutions orales de ketoprofène (300 mg/mL) et de paracetamol (200 mg/mL) et des poudres solubles de salicylate de sodium 100%, de paracetamol (200mg/g) et d'acide acétylsalicilique 100%.

Matériels et méthodes: Une solution de chaque produit a été préparée dans un réservoir de ferme de 300 L selon les instructions sur l'étiquette, sans agitation. Les concentrations d'ingrédient actif ont été déterminées par chromatographie liquide à haute performance sur trois échantillons prélevés à trois profondeurs standards dans le réservoir (haute, moyenne, et basse) à des temps de 5 minutes, 12 heures, et 24 heures suite à la préparation du mélange.

Résultats: Aucune différence statistiquement significative associée au temps n'a été observée dans les concentrations des principes actifs. Toutefois, des différences significatives furent détectées dans les échantillons prélevés à des profondeurs différentes pour le salicylate de sodium et la poudre et la solution de paracetamol. Une certaine variabilité fut également observée pour l'acide acétylsalicylique, mais les différences n'étaient pas statistiquement significatives. Les concentrations obtenues à tous les temps et profondeurs d'échantillonnage pour le ketoprofène s'approchaient des valeurs calculées, indiquant une meilleure homogénéité et stabilité dans l'eau de boisson.

Implications: Lorsque des AINS préparés dans des réservoirs d'eau de boisson sont utilisés pour traiter des animaux de ferme, une variabilité dans la dose peut survenir si l'eau n'est pas brassée adéquatement après l'ajout du médicament. Un manque d'homogénéité peut entraîner une surdose ou une sous-dose, augmentant ainsi le risque, respectivement, de réactions adverses et d'infractions pour résidus dans les carcasses ou la possibilité d'un manque d'efficacité. Cette situation est plus évidente lorsque le produit ajouté est une poudre soluble plutôt qu'une solution.

Drugs are often administered in drinking water to treat large groups of various livestock species under intensive farming conditions. This route of administration is less labor intensive and less stressful for the animals than individual administration by the parenteral route, which would also prove unfeasible in commercial poultry facilities[1] and many swine finishing farms. However, when products are administered in drinking water, the dose ingested by each animal may vary because of differences in individual drinking patterns.[2] In addition, if the concentration of the active ingredient fails to be homogenous at all times, both in the water tank and in the drinking troughs it supplies, individual overdosing or underdosing can easily occur, depending on distance of troughs from the water tank and the time of day at which the animal drinks. Hence, it is essential that the medication administered by this route be homogeneously dissolved in order to minimize the variability inherent to this administration route.

While medication administered through drinking water has great advantages, it also has disadvantages, including possible lack of solubility or stability of the drugs in different types of water.[1] Regulations in Europe for licensing of veterinary medicinal products stipulate that products administered in the drinking water must be proven soluble in both hard and soft water at temperatures from 4° to 20°C and must remain stable for 24 hours, which is the optimal period of administration while maintaining the hygienic quality of water.[3]

In 2005, KuKanich et al[4] reported the importance of both the formulation and the administration route of drugs from both a pharmacokinetic and residue viewpoint, which could lead to errors in withdrawal times. Dorr et al[5] reported the influence of water flow when tetracycline hydrochloride is administered by this route in pig farms, and its subsequent therapeutic effect. Toutain and Lees[2] and Santos et al[6] also related the variability of this administration route to the possible onset of resistance if antibiotic underdose were to occur. In addition to these factors, other sources of variability relate to use of dirty tanks and the addition of pH-modifying substances.[7]

Considering the risks described by these authors in connection with orally administered products, this study attempts to verify, under field conditions, the stability and homogeneity of concentrations of NSAIDs marketed in Europe as oral solutions or soluble powders and administered to finisher pigs in drinking water.

Materials and methods

The solubilities of five oral NSAIDs marketed in Europe for use in pigs were compared. The description of tested products is detailed in Table 1. In order to simulate product administration under field conditions, a solution of each product was prepared in a 300-L farm tank. Administration via dilution in bulk water tanks could be considered the worst case, compared with the much smaller and more readily managed volumes of concentrated stock solutions administered via proportioners. Active-ingredient concentrations were obtained by sampling at three tank depths, lower, middle, and upper, at 5 minutes, 12 hours, and 24 hours post mixing. All medicated water samples were frozen at -25°C ± 5.0°C until submitted to the analytical laboratory, suitably packaged in dry ice, for determination of active-ingredient concentrations.

Firstly, in order to facilitate its dissolution and following normal field practice, a predilution of each product was prepared by adding the total dose to be administered (in a final water volume of 300 L) to 10 L of water in a plastic bucket. This predilution was poured directly into a previously calibrated polyester and fiberglass tank (diameter 65 cm, height 100 cm) filled with water to 300 L. Neither predilutions nor final solutions were stirred after preparation during the entire experiment. The doses tested for each product, specified in Table 2, are those established to treat 50-kg pigs that drink 5 L of water a day. The water used in this trial was obtained from the water supply network of the city of Banyoles (Girona, Spain). Water was characterized as hard (758 mg $CaCO_3$ per L), pH 7.66, with free residual chlorine and combined residual chlorine of 0.3 mg per L and < 0.02 mg per L, respectively. Water temperature was maintained at 20°C throughout the trial.

In order to assess the homogeneity of the mixture prepared in the tank, 60-mL duplicate samples were obtained at three tank depths: lower, middle, and upper. For minimal interference during the sampling process, a plastic probe (diameter 0.5 cm) was attached to a 100-cm long rigid plastic rod that was marked at 5-cm intervals. Samples were collected by placing the rod on the tank bottom with the probe end attached at the desired depth. A syringe attached to the

probe at the water surface was used to aspirate the sample. The first aspirated water was discarded to avoid contamination with water from other levels.

Samples were obtained as follows: lower-depth sample at 5 cm from the bottom of the tank, middle-depth sample at 45 cm from the bottom, and upper-depth sample at 90 cm from the bottom (10 cm below the water surface). In order to assess homogeneity and stability for 24 hours, samples were collected serially at 5 minutes (initial time) and at 12 and 24 hours after preparation of medicated water.

Medicated water samples were analyzed by high-performance liquid chromatography (HPLC) using validated techniques and with a limit of quantitation set at 10 mg per L. Standards were prepared by first preparing solution S1 (0.025 g of paracetamol [Alfa Aesar, Ward Hill, Massachusetts] or 0.025 g of acetylsalicylic acid (ASA) [Sigma Aldrich, St Louis, Missouri]) made up to 25 mL with methanol, or 0.025 g of ketoprofen (Sigma Aldrich) made up to 25 mL with HPLC mobile phase. After solution S1 was prepared, a second dilution (S2) was prepared by making 1 mL of solution S1 up to 50 mL with HPLC mobile phase. Each water sample was passed through a filter (diameter 0.45 μm) and injected with the corresponding standard solution (S2) into the chromatograph. The chromatographic conditions for each product are described in Table 3.

Statistical analysis

In order to compare dispersion among the tested products, the concentration value obtained for each product was expressed as a percentage of the expected (calculated) concentration, and this percentage was used in the statistical analysis. A two-tailed ANOVA performed in SigmaStat (version 2.03, 1992-1997; SPSS Inc, Ashburn, Virginia) was used to compare the concentrations (percentages) obtained at the three time points (stability) and at the three measurement depths (homogeneity). Statistical significance was set at $P < .05$.

Results

Concentrations of the active ingredient in each product, expressed in mg per L of drinking water and as the percentage of the calculated concentration, are shown in Table 4. Figure 1 shows that homogeneity of the active ingredients differed with sampling location in the tank. Five minutes after preparation of medicated water, concentrations at the lower part of the tank exceeded the calculated values for all products except ketoprofen, ranging between an excess of 29% for paracetamol solution and 47% for

Table 1: Swine NSAID products tested for stability and homogeneity when prepared in drinking water at their therapeutic doses*

Product†	Declared composition		Dosage form
	Active ingredient	Excipients	
Ketoprofen	Ketoprofen 300 mg/mL	Arginin, benzyl alcohol, water	Oral solution
Sodium salicylate	Sodium salicylate 100%	None	Soluble powder
Paracetamol powder	Paracetamol 200 mg/g	Lactose monohydrate	Soluble powder
Paracetamol solution	Paracetamol 200 mg/mL	Macrogol 300	Oral solution
Acetylsalicylic acid	Acetylsalicylic acid 100%	None	Soluble powder

* The calculated dose of each product was first diluted in 10 L of water in a plastic bucket without stirring. The contents of the bucket were then poured into a 300-L tank filled with water, without stirring.

† Ketoprofen: Dinalgen/Danidol Oral Solution, Esteve veterinaria. Laboratorios Dr Esteve SA, Spain; sodium salicylate: Solacyl 100%, Eurovet Animal Health BV, the Netherlands; paracetamol powder: Pracetam Oral Powder, Sogeval Laboratoires, France; paracetamol solution: Pracetam Oral Solution, Sogeval Laboratoires, France; acetylsalicylic acid: ASA 100% Powder, Klat Chemie GmbH, Germany.

NSAID = nonsteroidal anti-inflammatory drug.

Table 2: Quantities of each of five swine oral NSAID products added to 300 L of water in a stock tank*

Product#	Therapeutic dose (mg/kg)	Target dosage for 50-kg pig (mg)	Quantity of product added to tank	Concentration of active ingredient (mg/L)
Ketoprofen	3	150	30 mL	30
Sodium salicylate	35	1750	105 g	350
Paracetamol powder	30	1500	450 g	300
Paracetamol solution	30	1500	450 mL	300
Acetylsalicylic acid	50	2500	150 g	500

* Products are described in Table 1. The concentration of each product in 300 L of water was based on the therapeutic dose of the active ingredient calculated to treat 50-kg pigs with a standard medicated-water consumption of 5 L per day. Each product was first diluted in 10 L of water in a bucket, without stirring; the contents of the bucket was then poured into the 300-L tank.

NSAID = non-steroidal anti-inflammatory drug.

Table 3: Chromatographic conditions for analysis of active ingredients in five NSAID products labeled for treatment of swine in drinking water*

	Active ingredient		
	Paracetamol	**Sodium salicylate and acetylsalicylic acid**	**Ketoprofen**
Volume (μL)	50	20	100
Mobile phase	Phosphate buffer (75%), methanol (25%)	0.01M acetic acid (60%), methanol (40%)	Phosphate buffer pH 2.5 (60%), acetonitrile (40%)
Flow rate (mL/minute)	1.0	1.0	1.0
Detector (nm)	245	280	233

* Medicated water samples were analyzed by high-performance liquid chromatography with a limit of quantitation of 10 mg/L of each active ingredient. The chromatography column in each case was a Waters Symmetry C18 (Waters, Milford, Massachusetts) (5μm) (3.9 × 150 mm). Each product was prepared in a 300-L tank to provide a dosage calculated for 50-kg pigs. Table 2 shows the calculated concentration of each active ingredient in the medicated water.

NSAID = nonsteroidal anti-inflammatory drug.

Table 4: Active ingredient concentrations found in medicated drinking water after NSAID products were added to a 300-L tank and water was left unstirred*

Product	Concentration of active ingredient (mg/L) (% of calculated concentration)									*P*†	
	5 minutes			12 hours			24 hours				
	Lower	**Middle**	**Upper**	**Lower**	**Middle**	**Upper**	**Lower**	**Middle**	**Upper**	**Time**	**Depth**
Ketoprofen	29.2 (97.4)	21.3 (71.2)	25.8 (86.1)	30.3 (101.1)	29.2 (97.4)	28.1 (93.6)	31.5 (104.9)	30.3 (101.1)	25.8 (86.1)	.82	.28
Sodium salicylate	510.1 (145.7)	300.0 (85.7)	58.4 (16.7)	498.9 (142.5)	395.5 (113.0)	118.0 (33.7)	482.0 (137.7)	280.9 (80.3)	137.1 (39.2)	.56	.002
Paracetamol powder	434.8 (144.9)	246.1 (82.0)	91.0 (30.3)	468.5 (156.2)	240.4 (80.1)	125.8 (41.9)	438.2 (146.1)	220.2 (73.4)	127.0 (42.3)	.20	< .001
Paracetamol solution	386.5 (128.8)	238.2 (79.4)	129.2 (43.1)	371.9 (124.0)	186.5 (62.2)	149.4 (49.8)	369.7 (123.2)	203.4 (67.8)	179.8 (59.9)	.70	< .001
Acetylsalicylic acid	737.1 (147.4)	325.8 (65.2)	289.9 (58.0)	783.1 (156.6)	370.8 (74.2)	415.7 (83.1)	415.7 (83.1)	359.6 (71.9)	374.2 (74.8)	.45	.07

* NSAID products, calculated concentrations of active ingredients, and analytical methods are described in Tables 1-3. Samples were collected at 5 minutes, 12 hours, and 24 hours after products were added to the water, and at three different depths: Lower, 5 cm from the bottom; Middle, 45 cm from the bottom; Upper, 90 cm from the bottom (10 cm below the water surface). Height of the tank, 100 cm.

† Statistical analysis was performed by ANOVA, with $P < .05$ considered statistically significant.

NSAID = non-steroidal anti-inflammatory drug.

ASA (Figure 1A). This tendency to overdose in the lower part of the tank persisted at the 12-hour reading, with percentages ranging between an excess of 1% for ketoprofen and 57% for ASA (Figure 1B). At the 24-hour reading, concentrations exceeded the calculated values by 46% for paracetamol powder, 38% for sodium salicylate, and 23% for paracetamol solution (Figure 1C). Concentration of ketoprofen exceeded the calculated value by only 5%, while concentration of ASA was only 83% of the calculated value.

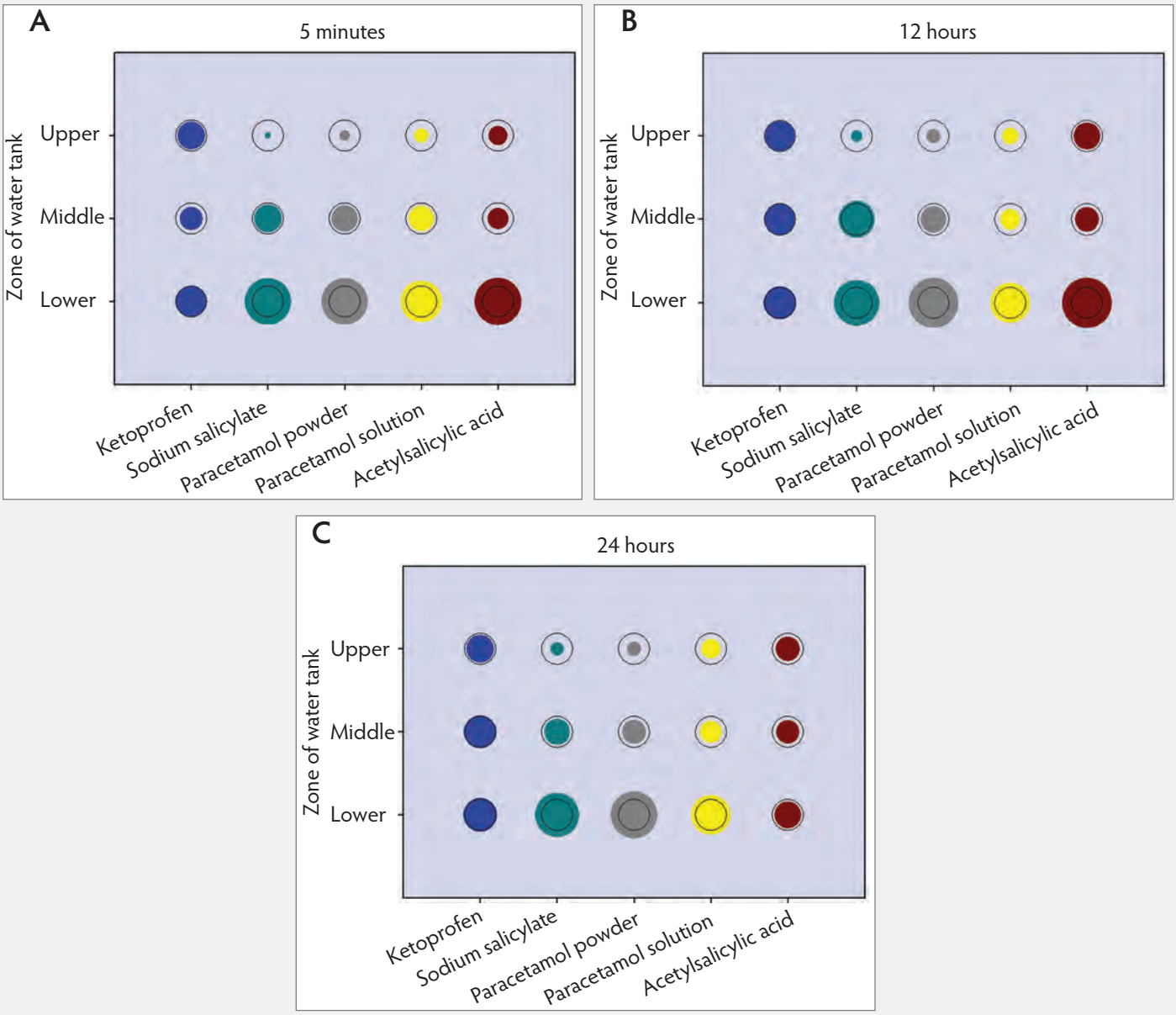
The concentration at any of the measurement levels (sampling depths) did not change significantly with time. However, concentrations of all ASA samples collected at 24 hours were below the calculated concentration, as shown in Figure 1.

While no statistically significant differences were observed among the five products, statistically significant differences among the three sampling depths were detected in concentrations of sodium salicylate, paracetamol solution, and paracetamol powder. Concentrations of ASA also varied among sampling depths, but the differences were not statistically significant ($P = .07$). The degree of dispersion of each product is depicted in Figure 2, which shows the concentrations obtained from the nine water samples analyzed for each product, regardless of sampling time.

Discussion

Because no significant time-related differences were observed, all products apparently

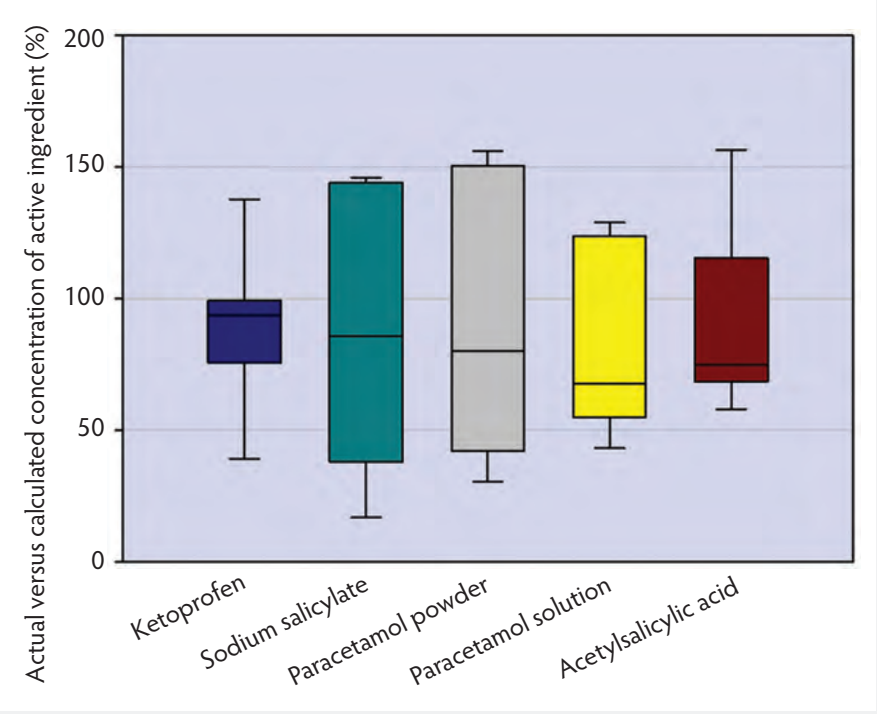
Figure 1: Active ingredient, as a percentage of the calculated concentration of each product, at three sampling depths in a 300-L water tank (1 m height) 5 minutes (A), 12 hours (B), and 24 hours (C) after five NSAID products were each mixed with water (products and protocols described in Tables 1 and 2, respectively). Sampling depth: Upper, 10 cm below water surface, 90 cm from the bottom of the tank; Middle, 45 cm from the bottom; and Lower, 5 cm from the bottom. Calculated concentration (100%) is represented by a black circle.



showed acceptable stability in drinking water. However, all ASA samples collected at 24 hours were below the calculated concentration, which might suggest that degradation of the active ingredient had occurred. Inserts of several commercial ASA products recently registered support this by stating that the stability of the product in drinking water is 12 hours.[8-10]

Significant differences were detected in the sampling-depth variable for all products except ketoprofen and ASA. For sodium salicylate, paracetamol powder, and paracetamol solution, concentrations increased significantly with increasing sampling depth. Under field conditions in Europe, the water distribution pipe usually takes the water from the lower part of the tank, thus results obtained at this depth are particularly important. The high values found at this depth of the tank forewarned that up to a 50% overdose might be reached, thereby increasing the risk of adverse events and violative residues in the carcasses. On the other hand, as the overdosed water is consumed during the day, at the end of the day water with lower concentration of active ingredient would be consumed. Therefore, an underdose might also occur if an individual animal drinks water late in the day, thus increasing the possibility of lack of efficacy. In the case of ASA, the absence of significant differences at different sampling depths, despite its apparent high dispersion at the 5-minute and 12-hour time points, may be due to excessive variability for such a limited number of analyzed samples. Overall results showed that ketoprofen had the best dissolution and lowest variability among all tested products.

Figure 2: Variability observed (median and percentiles) in active ingredient as a percentage of the calculated concentration of samples of five NSAID products, each diluted in water without stirring (products and protocols described in Tables 1 and 2, respectively). Samples were collected at 5 minutes, 12 hours, and 24 hours post administration at three depths in a 300-L water tank (nine samples per product): Upper, 10 cm below water surface (90 cm from the bottom of the tank); Middle, 45 cm from the bottom; and Lower, 5 cm from the bottom. Samples were analyzed by high-performance liquid chromatography.



In general, no relevant differences were observed between soluble-powder formulations and oral solutions. However, the better behavior of ketoprofen solubility versus the other oral solution formulation, paracetamol solution, could be because the active ingredient of ketoprofen dissolves in water, while paracetamol solution is dissolved in the excipient, a polyethylene glycol derivative, which in turn must dissolve when the product is added to water. In the case of the ketoprofen product, the active ingredient is already diluted in water, and thus immediately dissolves in the whole tank volume. It is likely that thoroughly stirring the tank water after product addition would have been advantageous for the other products. In this trial, however, products were added without stirring in order to simulate the most unfavorable and authentic conditions on a commercial farm. The need for stirring is not mentioned in the instructions for use (labeling) of any of the products tested.

Concentrations of ketoprofen most closely approached the calculated concentration at all time points and sampling depths, evidencing better homogeneity and stability in drinking water. Thus ketoprofen might be considered the gold standard when the behavior of other currently available or future NSAID products for drinking water use are compared.

Implications

- The use of NSAIDs in drinking water for treatment of farm animals can result in overdosing or underdosing when the concentration of drug varies in different areas of the tank.
- Overdosing may increase the risk of adverse events and violative residues in the carcasses, while lack of efficacy may occur when a product is underdosed.
- Lack of homogeneity is more evident when the added product is a soluble powder rather than a solution.

References

1. Vermeulen B, De Backer P, Remon JP. Drug administration to poultry. *Adv Drug Del Rev*. 2002;54:795–803.

2. Toutain PL, Lees P. WS04 The population PK/PD approach for a rational use of anti-infective drugs to minimize resistance. *J Vet Pharmacol Ther*. 2006;9(suppl 1):26–29. doi: 10.1111/j.1365–2885.2006.00773_4.x.

3. EMEA/CVMP/540/03 Rev 1: Guideline on Quality Aspects of Pharmaceutical Veterinary Medicines for Administration Via Drinking Water. European Medicines Agency, Committee for Veterinary Medicinal Products, 2005. Available at: **http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/10/WC500004462.pdf**. Accessed 10 August 2012.

4. KuKanich B, Gehring R, Webb AI, Craigmill AL, Riviere JE. Effect of formulation and route of administration on tissue residues and withdrawal times. *JAVMA*. 2005;227:1574–1577.

5. Dorr PM, Nemechek MS, Scheidt AB, Baynes RE, Gebreyes WA, Almond GW. Water-flow variation and pharmacoepidemiology of tetracycline hydrochloride administration via drinking water in swine finishing farms. *JAVMA*. 2009;235:299–304.

6. Santos MD, Vermeersch H, Remon JP, Schelkens M, De Backer P, Ducatelle R, Haesebrouck F. Administration of doxycycline hydrochloride via drinking water to turkeys under laboratory and field conditions. *Poult Sci*. 1997;76:1342–1348.

7. Dorr PM, Madson D, Wayne S, Scheidt AB, Almond GW. Impact of pH modifiers and drug exposure on the solubility of pharmaceutical products commonly administered through water delivery systems. *J Swine Health Prod*. 2009;17:217–222.

8. AEMPSa (Spanish Agency of Medicines and Sanitary Products) Summary of Product Characteristics document for Vetalgine [in Spanish]. Available at: **https://sinaem4.agemed.es/consavet/especialidad.do?metodo=verFichaWordPdf&codigo=1913 ESP&formato=pdf&formulario=FICHAS**. Accessed 10 August 2012.

9. AEMPSb (Spanish Agency of Medicines and Sanitary Products) Summary of Product Characteristics document for Apirex [in Spanish]. Available at: **https://sinaem4.agemed.es/consavet/especialidad.do?metodo=verFichaWordPdf&codigo=1969 ESP&formato=pdf&formulario=FICHAS**. Accessed 10 August 2012.

10. AEMPSc (Spanish Agency of Medicines and Sanitary Products) Summary of Product Characteristics document for Fatrospirina [in Spanish]. Available at: **https://sinaem4.agemed.es/consavet/especialidad.do?metodo=verFichaWordPdf&codigo=1878 ESP&formato=pdf&formulario=FICHAS**. Accessed 10 August 2012.