Comparative single intraperitoneal dose pharmacokinetics of aspirin and acetaminophen in chicks

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ABSTRACT: Limited information is available on the pharmacokinetics and bioavailability of aspirin and acetaminophen in young chicks. The purpose of the present study was to examine the pharmacokinetics of acetyl salicylic acid (aspirin) and acetaminophen in 12-day old chicks after a single intraperitoneal administration of each drug alone at the dose of 100 mg/kg body weight. Blood samples were collected from chicks (six/each time period) at 10, 20, 30, 60 and 120 min after each drug administration. The concentrations of aspirin and acetaminophen in the plasma were determined by spectrophotometric methods. The pharmacokinetic parameters of the drugs were calculated by a non-compartmental analysis. The elimination half-lives of aspirin and acetaminophen were 1.68 and 1.36 h with steady state volume of distributions 0.079 and 1.11 l/kg and total body clearances of 0.029 and 0.53 l/h/kg, respectively. The mean residence times of the drugs were 2.74 and 2.09 h and their area under the plasma concentration-time curves (0–∞) were 3486 and 188 μg·h/ml, respectively. In conclusion, the data show the pharmacokinetic profiles of single intraperitoneal doses of aspirin and acetaminophen in chicks and suggest that acetaminophen is well distributed in the body of the chicks and eliminated faster from the body compared to aspirin. These parameters should be taken into consideration in further therapeutic and toxicological studies of drugs in chickens.

Keywords: aspirin; acetaminophen; pharmacokinetics; chicken; bioavailability

Acetyl salicylic acid (aspirin) and acetaminophen are non-steroidal analgesics commonly used in veterinary practice (Livingston 2010; Miller and Richardson 2011) with some uses in the avian medicine (Machin 2005; Hawkins and Paul-Murphy 2011). The therapeutic actions of these drugs include analgesic, antipyretic and small anti-inflammatory effects (Livingston 2010; Hawkins and Paul-Murphy 2011; Miller and Richardson 2011). In poultry, aspirin may be used as an anti-stress agent (McDaniel and Parker 2004). Acetaminophen and aspirin are also used in the chicken to induce certain models of toxicity which requires knowledge of their distribution and pharmacokinetics (Lambert et al. 1986; Murai et al. 1994; Mohan et al. 2008).

Limited information is available on the pharmacokinetics and bioavailability of aspirin and acetaminophen in young chicks (Lambert et al. 1986; Baert and De Backer 2003). Baert and De Backer (2002, 2003) have reported the pharmacokinetic parameters of sodium salicylate after intravenous administration in adult chickens. A recent study reported several pharmacokinetic parameters of acetaminophen in the chicken after intravenous and oral administration of 10 mg/kg (Neirinckx et al. 2010). The purpose of the present study was to examine the pharmacokinetics of aspirin and acetaminophen in 12-day old chicks after a single intraperitoneal administration at a dose of 100 mg/kg body weight.

MATERIAL AND METHODS

Mixed breed broiler chicks of either sex (12 days old, body weight 100–112 g) were used. They were maintained in batches of 30 chicks in a room at a temperature of 30–34 °C with constant lighting. An

injectable source of acetylsalicylic acid (lysine acetylsalicylic acid; Aspegic, Synthelabo, France) was dissolved in water for injection to prepare 100 mg of aspirin/5 ml/kg body weight. Acetaminophen was kindly donated by the State Company for Drugs and Medical Appliances, Samarra, Iraq. It was dissolved in 40% aqueous solution of propylene glycol at 100 mg/5 ml/kg body weight. Each chick was either treated with aspirin or acetaminophen intraperitoneally (*i.p.*). The doses of the drugs were based on preliminary experiments in which they did not produce overt signs of toxicosis in chicks and the birds tolerated doses of aspirin and acetaminophen up to 150 mg/kg, *i.p.*

Blood samples (1–2 ml) were collected from chicks (6/each sampling time) at 10, 20, 30, 60 and 120 min after each drug administration. Plasma was separated from erythrocytes by centrifugation of blood samples at 3000 rpm (Centurion, U.K.) for 15 min. Plasma samples were stored at –18 °C pending analysis within 48 h. Spectrophotometric methods were used to measure the concentrations of aspirin (Keller 1947; Jarvie et al. 1987) and acetaminophen (Archer and Richardson 1980) in the plasma samples. Because of the wide individual variations in the plasma concentrations of the drugs in the chicks, means of plasma concentrations of aspirin and acetaminophen at each sampling time (10–120 min) were used to calculate the pharmacokinetic parameters by a non-compartmental analysis (Perlin et al. 1985; Levy and Bauer 1986) using a Windows-based computer program (Laub and Gallo 1996). Calculations included the following pharmacokinetic variables: area under plasma concentration-time curve ($AUC_{0-\infty}$) and area under the moment curve ($AUMC_{0-\infty}$) from time zero to infinity, elimination half-life ($t_{1/2ß}$), elimination rate constant ($k_{el} = 0.693/t_{1/2ß}$), steady state volume of distribution [V_{ss} = Dose × AUMC/$(AUC)^2$], maximum drug concentration (Cmax), time to maximum drug concentration (Tmax), mean residence time (MRT = AUMC/AUC) and total clearance (CL = Dose/AUC). Acetaminophen and aspirin concentrations at each sampling time were subjected to statistical analysis using an unpaired Student's-*t*-test. The level of significance was set at $P < 0.05$.

The study was approved by the Scientific Committee of the College of Veterinary Medicine at the University of Mosul, Iraq. All experiments complied with regulations addressing animal use, and proper attention and care was given to the chicks used in the study.

RESULTS AND DISCUSSION

Salicylic acid was detected in the plasma at mean concentrations ranging between 764–1443 µg/ml and acetaminophen at 36.3–86.3 µg/ml 10–120 min after *i.p.* administration in chicks (Table 1). Acetaminophen concentrations were significantly lower than those of aspirin at sampling times ranging between 10 and 120 min (Table 1). The pharmacokinetic variables of aspirin and acetaminophen in chicks are shown in Table 2. The Tmax times of aspirin and acetaminophen were 0.75 and 0.33 h, respectively, indicating that absorption into the systemic circulation is not instantaneous in spite of the high absorption capacity of the peritoneal cavity. The elimination half-lives of aspirin and acetaminophen were 1.68 and 1.36 h with steady state volume of distributions of 0.079 and 1.11 l/kg and total body clearances of 0.029 and 0.53 l/h/kg, respectively. The mean residence times of the drugs

Table 1. Plasma salicylic acid and acetaminophen concentrations in chicks after single intraperitoneal administration of the drugs at 100 mg/kg body weight

Time (min)	Salicylic acid (µg/ml)	Acetaminophen (µg/ml)
10	827 ± 338	58.92 ± 8.32*
20	1196 ± 374	86.33 ± 5.43*
30	1422 ± 577	76.43 ± 6.94*
45	1443 ± 391	70.93 ± 5.47*
60	906 ± 180	63.28 ± 7.90*
120	764 ± 192	36.33 ± 5.14*

Values are mean ± SE of plasma drug concentrations of six chicks/each sampling time
*significantly different from the respective value of salicylic acid, $P < 0.05$

Table 2. Pharmacokinetic parameters of aspirin and acetaminophen in chicks following a single intraperitoneal administration at a dose of 100 mg/kg body weight

Variable*	Aspirin	Acetaminophen
Mean residence time (h) (MRT = AUMC/AUC)	2.74	2.09
Steady state volume of distribution (l/kg) (V_{ss} = Dose × AUMC/(AUC)^2)	0.079	1.11
Elimination rate constant (h^{-1}) (k_{el} = 0.693/$t_{1/2ß}$)	0.41	0.51
Elimination half-life (h) ($t_{1/2ß}$)	1.68	1.36
Tmax (h)	0.75	0.33
Cmax (µg/ml)	1443.0	86.33
Total clearance (l/h/kg) (CL = Dose/AUC).	0.029	0.53
Area under plasma concentration-time curve (µg·h/ml) ($AUC_{0-\infty}$)	3486	188
Area under the moment curve (µg·h^2/ml) ($AUMC_{0-\infty}$)	9542	393

*the means of plasma concentrations of the drugs at each sampling time (10–120 min) were used to calculate the pharmacokinetic parameters by a non-compartmental analysis using the Windows-based computer program (Laub and Gallo 1996); n = 6 chicks/each sampling time

were 2.74 and 2.09 h and their area under the plasma concentration-time curves (0–∞) were 3486 and 188 µg·h/ml, respectively. Other related pharmacokinetic parameters are also shown in Table 2.

The pharmacokinetic data of the present study suggest that acetaminophen is well distributed in the body of the chicks (Vd 1.11 vs 0.079 l/kg) and eliminated faster from the body compared to aspirin. V_{ss} is a reliable estimate of the volume of drug distribution, since it is calculated independently of the k_{el} (Perlin et al. 1985; Levy and Bauer 1986). The slow elimination of aspirin from the body may favour prolonged therapeutic or possible toxic actions of the drug (Machin 2005; Livingston 2010; Hawkins and Paul-Murphy 2011). The low volume of distribution of aspirin could be related to the relatively high (up to 90%) plasma protein binding of salicylate (Davis and Westfall 1972). The low plasma protein binding of acetaminophen together with its small molecular size favours distribution of the drug into the tissues (Bannwarth and Pehourcq 2003). However, animal species differ in their metabolism and plasma clearance of aspirin and acetaminophen (Davis and Westfall 1972; Livingston 2010; Neirinckx et al. 2010). The differences between acetaminophen and aspirin concentrations in the plasma of the chicks could be attributed to the differences in the absorption rate, distribution, plasma protein binding and metabolism pattern between the two drugs (Davis and Westfall 1972; Livingston 2010; Neirinckx et al. 2010; Hawkins and Paul-Murphy 2011).

The pharmacokinetic parameters of aspirin and acetaminophen ($t_{1/2ß}$, V_{ss} , CL, AUC, etc.) as determined in the present study in chicks are not found collectively in the literature concerning avian species (Davis and Westfall 1972; Lambert et al. 1986; Baert and De Backer 2002, 2003; Neirinckx et al. 2010). The plasma half-life of acetaminophen ranges between 1–4 h across various species which could increase in cases of overdose (St. Omer and Mohammad 1984; Bannwarth and Pehourcq 2003; Neirinckx et al. 2010). Sodium salicylate administration in birds resulted in a plasma half-life of salicylic acid in the chicken (3.13 h) which was shorter than those in the pigeon and duck (Baert and De Backer, 2003). Neirinckx et al. (2010) reported the pharmacokinetics parameters of acetaminophen in five-week old chickens after intravenous and oral administration (10 mg/kg). Comparing the findings of the latter studies in the chicken (Davis and Westfall 1972; Lambert et al. 1986; Baert and De Backer 2002, 2003; Neirinckx et al. 2010) with those of the present one in chicks, the variations in absolute pharmacokinetic values could be attributed to the differences in the dosage, route of administration, dosage form and formulation as well as the age of the birds (Baert and De Backer 2002, 2003; Machin 2005; Hawkins and Paul-Murphy 2011).

CONCLUSIONS

As there is limited information on the pharmacokinetics of aspirin and acetaminophen in chicks, the present findings suggest variations in plasma concentrations vs. time curves as well as the re-

lated pharmacokinetic parameters between the two drugs. Acetaminophen is well distributed in the body of the chicks and eliminated faster from the body compared to aspirin. The comparative pharmacokinetic aspects of the two drugs should be taken into consideration in therapeutic and toxicological studies of these drugs in young chicks.

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MOHAMMAD, F.K., MANSOOR, A.S. and AL-ZUBAIDY, M.H.I. (2012) Comparative single intraperitoneal dose pharmacokinetics of aspirin and acetaminophen in chicks. Veterinari Medicina 57: 121-124.Google Scholar. MOHAMMED, A.A. (2010) Effect of acetyl salicylic acid (ASA) in drinking water on productive performance and blood characteristic of layer hens during heat stress. International Journal of Poultry Science 9: 382-385.Google Scholar.Â TRAÅž, B., INAL, F., BAÅž, A., ALTUNOK, V.L., ELMAS, M. and YAZAR, E. (2000) Effect of continuous supplementation of ascorbic acid, aspirin, vitamin E and selenium on some haematological parameters and serum superoxide dismutase level in broiler chickens. British Poultry Science 41: 664-666.CrossRef Google Scholar PubMed. Since the dosage regimens are often designed based on pharmacokinetic analysis of a single administration, it may be well advised to reassess some drugs in terms of their pharmacokinetics after repeated administration. This may be of particular interest if clinical effects of a given drug seem to decline with time.Â Comparative single intraperitoneal dose pharmacokinetics of aspirin and acetaminophen in chicks. Vet Med Czech. 2012;57: 121â€“124. View Article. Google Scholar. 9. PoÅºniak B, ÅšwitaÅ‚a M, Jaworski K, Okoniewski P, NiewiÅ„ski P. Comparative pharmacokinetics of acetylsalicylic acid and sodium salicylate in chickens and turkeys. Br Poult Sci. 2013;54: 538â€“544. pmid:23906222. Keywords: Comparative Pharmacokinetics of Aspirin / Pharmacokinetics of Aspirin and Acetaminophen. Scifeed alert for new publications. Never miss any articles matching your research from any publisher. Get alerts for new papers matching your research. Find out the new papers from selected authors. Updated daily for 49'000+ journals and 6000+ publishers. Define your Scifeed now. Ã—. Pharmacokinetics and Pharmacodynamics of Acetaminophen and Aspirin; By Vincenzo Crawford. Download. Pharmacokinetics and Pharmacodynamics of Acetaminophen and Aspirin; By Vincenzo Crawford. Vincenzo D Crawford. PHARMACODYNAMICS OF ASANSAIDs such as aspirin benefits some patients greatly in alleviating their discomforts caused by pain, inflammation, fever, etc. However, serious side effects can occur and generally tend to be dose related. Therefore, it is advisable to use the lowest effective dose to minimize side effects.The most common side effects of aspirin involve:1. Stomach ulceration and bleeding can occur without any abdominal pain. 2. Black tarry stools, weakness, and dizziness upon standing may be the only signs of internal bleeding.