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Age-Related Changes in Ouabain Pharmacokinetics†

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= Abstract =Young animals and humans frequently require higher doses of digitalis glycoside per kilogram of body weight or per square meter of body surface area than adult to induce the digitalis effect or toxicity. In order to investigate the pharmacokinetic basis for this observation, we studied pharmacokinetic properties of the relatively polar and rapidly acting cardiac glycoside, ouabain, in adult and young rabbits. Consistent with reported observations, we found no significant difference in transfer coefficients in a linear two compartmental open model for ouabain pharmacokinetics following a 0.05 mg/kg bolus. However, we found that young rabbits had larger ouabain volume of distribution per kilogram of body weight than adults (Vc; 274.36±24.24(S.E.) ml/kg vs. 138.29±7.51, Vdss; 1580.61±75.77 ml/kg vs. 1056.01±88.18, $p<0.005$), and a larger systemic clearance (9.18±0.74 ml/kg/min vs. 4.67 ±0.80, $P<0.01$). One could account for this difference by the fact that adult rabbits had nearly twice the serum concentrations at the same dose per kilogram, throughout the experimental period. Left and right ventricular ouabain concentrations were inversely related to the volumes of distribution, with significantly higher tissue levels in adult animals.

Although the reason for the difference of tissue sensitivity to a given digitalis glycoside concentration remains unclear, the result of this study suggests that the pharmacokinetic difference is responsible for age-related tolerance to digitalis glycoside doses.

Key Words: ***Ouabain, Digitalis glycoside, Rabbits, Pharmacokinetics, Two-compartment model, Serum level, Urinary excretion, Age-related changes, Mechanism of tolerance***

INTRODUCTION

It is well known that children and immature animals require more digitalis per kilogram of body weight than adults to achieve similar effective digitalis therapy (Cree et al. 1973; Levine and Blumenthal 1962; Wollenberger et al. 1952). This digitalis tolerance in children might include two potential mechanisms; age-related pharmacokinetic differences in absorption, distribution or elimination, which may produce concentration difference at the receptor site, and age-related pharmacodynamic differences, which could be result of changes of affinity or number of cardiac glycoside receptor during the developmental phase.

Several workers have looked at the second aspect. Specifically they studied the response at a given concentration, and compared the efect of digitalis on *in vitro* myocardial tissue preparation or $Na^+ - K^+ -$ATPase, the putative pharmacological receptor for digitalis glycosides (Akera et al. 1969; Goldman et al. 1973; Schwartz et al. 1974). Rosen et al. (1975) reported that purkinje fibers from young dogs were less sensitive to digitalis than those from adult animals. A preliminary report by Miller and Gilland (1972) stated that newborn dogs had significantly higher $Na^+ - K^+ -$ATPase activity measured by phoshate release from ATP. However, at the same time Atwood and Dunkley (1972) reported that newborn and adult sheep had the same myocardial enzyme activity, as estimated by phosphate release and ouabain binding. Marsh et al. (1981), recently, reported age dependent changes of myocardial $Na^+ - K^+ -$ATPase activity and specific ouabain binding in dog and guinea

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pigs. We reevaluated the differences of myocardial $Na^+ - K^+ -$ATPase activity and digoxin binding in young and adult dogs, but could not find no significant difference (Shin et al. 1985).

To explain the age-related differences in digitalis sensitivity, we studied pharmacokinetics of ouabain, a short acting cardiac glycoside, in young and adult rabbits. Our study deals only with the first potential mechanism of age-related differences in sensitivity. It explains why it is necessary to administer nearly twice the dose of digitalis per kilogram of body weight in children in order to achieve the same serum concentration as in adults, despite a lack of difference in digitalis metabolism and excretion between children and adults (Dungan et al. 1972; Iliaso and Dahl 1974).

METHODS

Our study group consisted of six adult rabbits, average weight 2.90±0.22(SD) kg and five 4 weeks old rabbits, average weight 0.77±0.07 kg. All animals were anesthetized by first administering sodium pentobarbital, 30 mg/kg, intravenously, followed by supplementary doses as needed. A polyethylene catheter within the carotid artery, connected to a pressure transducer, permitted blood sampling and systemic pressure monitoring. A catheter in the marginal vein of the ear was used for drug administration. Rectal temperature was maintained constant with a heating pad. Lead II of the electrocadiogram was used to record heart rate and rhythm.

After obtaining control blood samples, we administered an intravenous bolus (0.05 mg/kg) of randomly labeled ^{3}H-ouabain (New England Nuclear, specific activity 11.7 Ci/mmol), diluted to 30-50 uCi/mg with crystalline ouabain octahydrate.

Blood samples (0.8 ml) in adult rabbits were obtained at 1.17, 5, 10, 20, 40, 60, 90, 120 160, 200 and 240 minutes. To minimize blood and volume loss, we took blood samples at 1.17, 5, 10, 30, 90, 120, 160, 240 minutes from young animals. All blood was replaced with equal volumes of 6% dextran 70 in normal saline. Hematocrit was measured before injecting the ouabain, but the values did not differ in adult (37.6±1.4%) and young rabbits (37.5±1.5%). blood samples were centrifuged to seperate the serum. Urine collections were made every 30 minutes after ouabain administration.

Serum and urine samples were stored at -20°C for subsequent analysis. Experimental animals were killed after 240 minutes. As soon as each rat was killed, the left ventricle, right ventricle, liv spleen, kidney and thigh muscle were remov blotted dry and frozen for later analysis.

1. Measurement of serum and tissue ouab concentrations:

Since ouabain undergoes little metabolic conv sion prior to renal excretion (Laherty et al. 19 Marks et al. 1964; Selden et al. 1974), radioactivities emerging from serum and tiss were considered to represent unaltered ouba We determined serum and urine ouabain conc tration by adding 0.3 ml samples to 15 ml of dioxane based liquid scintillation cocktail (4 PPO, 0.242 gm POPOP, 60 gm naphthalene, 1 ml methanol, 20 ml ethylene glycol per liter). T and half mililiter concentrated nitric acid v added to 500 mg wet weight tissue, and incuba to be digested for 30 minutes at 70°C. (Pfeffer al. 1971). Digested samples were neutralized pH 7.4 with 0.75 M Tris. The digested 0.2 ml sc tions were added to 15 ml of the dioxane ba liquid scintillation cocktail. Then all samples w stored at 10°C in the dark before counting u chemoluminiscence had fully decayed. All samp were counted in a Packard liquid scintillation c ter to accumulate at least 4,000 cpm. (3% er The atuomatic external standards channel method was used to determine efficiency counting.

2. Data Analysis:

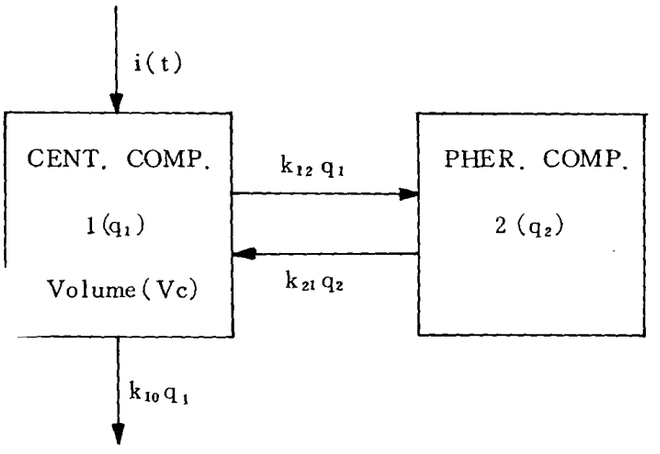
1) Pharmacokinetic analysis of serum oua concentrations

The changes in serum ouabain concentratior ter administering a bolus of ouabain intravenou were analyzed according to a linear two-comp ment open model (Fig. 1).

Serum ouabain concentration declines in the b ponential manner,

$$c(t)=Ae^{-\alpha t}+Be^{-\alpha t} \qquad (1)$$

where c(t) is serum concentration at given t and A, B, α, β, are constants, characteristic drug distributed according to the model. The bain bolus enters the central compartment volume (Vc) at time zero. The central compartn includes the plasma volume and other physiolo fluid spaces in rapid equilibrium with plas Metabolism, excretion, and distribution to perip al tissue compartment in slow equilibrium plasma remove ouabain from the plasma in prc tion to the mass (qi) of drug in equilibrium intercompartment transfer coeficinet (k_{10}, K_{12}, I



ig. 1. Linear two-compartmental model for ouabain Pharmacokinetics. qi. mass of drug, ki; intercompartment transfer coefficients.

ıe steady-state volume of distribution (Vdss) ıuals the total quantity of drug in the body di-ıed by the concentration in the reference region the central compartment at the time these ɔasurements are taken with the tissue compart-ɔnt containing the maximum amount of drug. ss is an independent constant only when eli-nation occurs exclusively from the central compartment. We fitted the observed serum ouabain concentration for each rabbit using equation (1) by the iterative least square non-linear curve fitting method (Lim et al. 1984).

To normalize the effect of differing error of ouabain serum concentration at each time, we weighted each point in inverse proportion to the variance of the measured serum concentration of each group of rabbits at that time (Table 1). This procedure weights noisy point less than more precisely known points. By using estimated A,B, α, β we computed Vc, Vdss, K_{10}, K_{12}, and K_{21} with following equations, (2)~(6) (Benet and Galeazzi 1979; Gibaldi and Perrier 1981)

$$Vc=\frac{Dose}{(A+B)} \quad (2)$$

$$Vdss=\frac{Dose(A/\alpha^2+B/\beta^2)}{(A/\alpha+B/\beta)^2} \quad (3)$$

$$K_{21}=\frac{A\beta+B\alpha}{A+B} \quad (4)$$

$$K_{10}=\frac{\alpha\beta}{K_{21}} \quad (5)$$

$$K_{12}=\alpha+\beta-K_{21}-K_{10} \quad (6)$$

Rt and Rs, the time constants for rapid distribution (α) and eliminaion phase(β), were calculated with $Rt=-\frac{1}{\alpha}$, and $Rs=-\frac{1}{\beta}$. They represent the slope of each phase.

ıable 1. Serum ouabain concentrations

Time (min)	Serum Oubain Concentration (ng/ml)				p**	Weights	
	Adult Rabbit(6)*		Young Rabbit(5)				
	Mean	±S.E.	Mean	±S.E.		Adult	Young
1.17	341.60	±19.11	153.64	±10.72	<0.0025	0.0018	0.007
5	133.93	±17.55	73.01	± 5.59	< 0.025	0.0027	0.026
10	83.72	± 9.95	40.79	± 1.79	<0.0025	0.0084	0.25
20	49.70	± 4.76	—	—		0.037	—
30	—	—	21.77	± 1.68		—	0.28
40	33.84	± 2.75	—	—		0.11	—
60	27.22	± 1.66	—	—		0.30	—
90	24.19	± 1.19	13.49	± 0.65	<0.0025	0.59	1.9
120	20.66	± 1.38	—	—		0.44	—
160	18.94	± 1.65	10.89	± 0.75	<0.0025	0.31	1.4
200	17.57	± 1.89	—	—		0.23	—
240	16.45	± 1.42	8.30	± 0.77	<0.0025	0.41	1.0

* Number of experimental animals

** To test the hypothesis that adult concentrations are greater than young dog concentrations, we used one-tail t-ɔst.

2) Ouabain clearance

Systemic and renal clearance of ouabain in experimental rabbits were determind by employing following equations,

$$Cls = Dose\ I.V/AUC \quad (7)$$

$$Clr = Xu_{t1}^{t2} / AUC_{t1}^{t2} \quad (8)$$

where Cls systemic clearance and clr is renal clearance. AUC represents the total area under the serum drug concentraion time curve and AUC_{t1}^{t2} is the area during the time interval t_1 to t_2 at which urine collections were made. The term of Xu_{t1}^{t2} is the amount of unmetabolized drug eliminated in urine during the time interval t_1 to t_2. The area under the curve (AUC) over a finit time or to infinity was calculated by direct integration for the individual equation derived by iterative fitting. Non-renal clearance was calculated by substrating renal clearance from systemic clearance. Renal excretion rate constant (Kre) of individual rabbit was calculated by the equation (9).

$$Kre = Clr/Vc \quad (9)$$

RESULTS

1. Serum Ouabain Concentrations:

After the administration of an ouabain dose of 0.05 mg per kilogram body weight; serum ouabain concentration fell according to biexponential cruves (Fig. 2). The concentration in adult rabbits was always significantly higher than that in young rabbits during the 240 minutes experimental period (Table 1). Serum concentration-time curves of young and adult rabbits do not show a significant departure from pararellism, indicating the concentration curves have the same shape and the same mean transfer coefficients. To verify this suggestion, we fitted the ouabain serum concentration-time curve with Equation (1) and computed the pharmacokinetic parameters for each rabbit seperately. Table 2 shows no significant difference in mean K_{10}, K_{12} or K_{21} between adult and young rabbits. And therefore time constants (Rt and Rs) for the two phases of young and adult rabbits were not significantly different. Mean serum half-life of ouabain for each phase in adult and young rabbits were 3.8 min., 184.8 min. and 3.3 min, 164.7 min, respectively. But the volume of central compartment (Vc) and the steady-state volume of distribution (Vdss) in

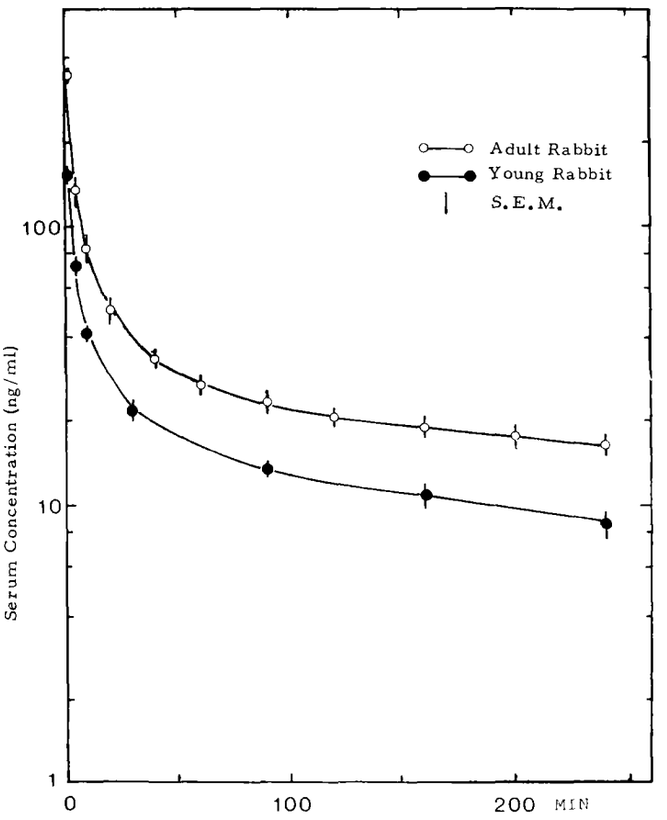


Fig. 2. Serum ouabain concentrations affter a dose of ouabain of 0.05 mg/kg. Ouabain concentration is plotted as ng/ml on the vertical axis on a semilogarithmic scale, time on the horizontal axis.

Table 2. Pharmacokinetic parameters for ouabain

(Mean ± S.E.)

Parameters	Adult Rabbit(n=6)	Young Rabbit (n=5)
Vc	138.29±7.51 ml/kg	274.36±24.24 ml/kg*
Vdss	1056.01±88.18 ml/kg	1580.61±75.77 ml/kg*
Rt	5.46±0.60 min	4.71±0.29 min
Rs	266.63±20.86 min	237.70±10.53 min
k_{10}	0.0345±0.0035 min^{-1}	0.0329±0.0022 min^{-1}
k_{12}	0.1520±0.0297 min^{-1}	0.1573±0.0120 min^{-1}
k_{21}	0.0225±0.0033 min^{-1}	0.0275±0.0009 min^{-1}

$p<0.005$, comparing adult with young rabbit values.

young rabbits were significantly ($P<0.005$) larger than those in adults. Since we administered the same dose of ouabain per kilogram to all rabbits, differences in volume of distribution account for the difference in serum ouabain concentration between adult and young rabbits. These data indicate that the serum ouabain concentration in young rabbits is lower than that of adults because the drug mass in equilibrium with plasma is diluted in a greater volume.

2. Renal Elimination of Ouabain:

Renal excretion of ouabain during 240 minutes experimental period was determined in 4 experimental animals for each age group. Urinary excretion amount at a given time was calculated from urine amount and measured concentration. Fig. 3 shows mean cumulative excretion amount of ouabain through kidney. There was no significant difference in cumulative percent of dose in urine between adult and young rabbits. During 240 minutes of experimental period, urinary excretion fraction of ouabain was 40.5 to 43.5 percent of administered dose in adults, and 31.8 to 47.7 percent in young of rabbits. Clearances of ouabain, calculated from AUC and urinary excreted ouabain amounts shows a significant difference between adult and young rabbits (Table 3). Whereas urinary excretion rate

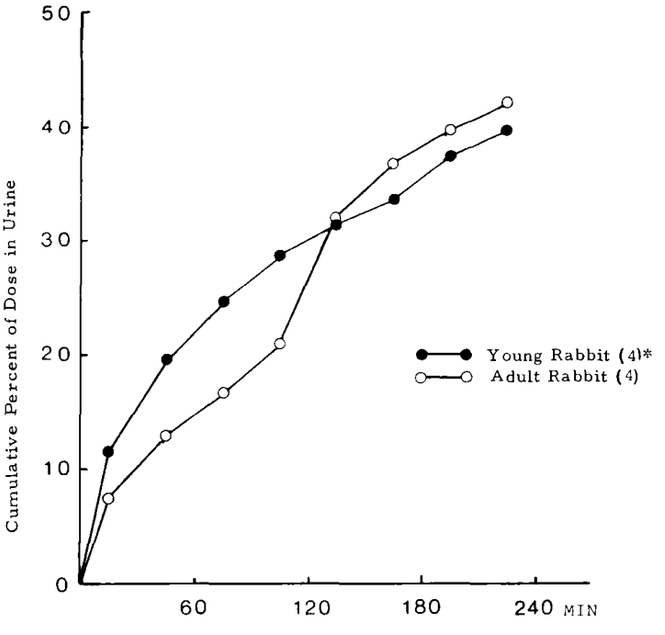


Fig. 3. Mean urinary excretion of cuabain. Cumulative urinary excretion plotted for 240 min after a dose of 0.05 mg/kg ouabain.*; Number of experimental animals.

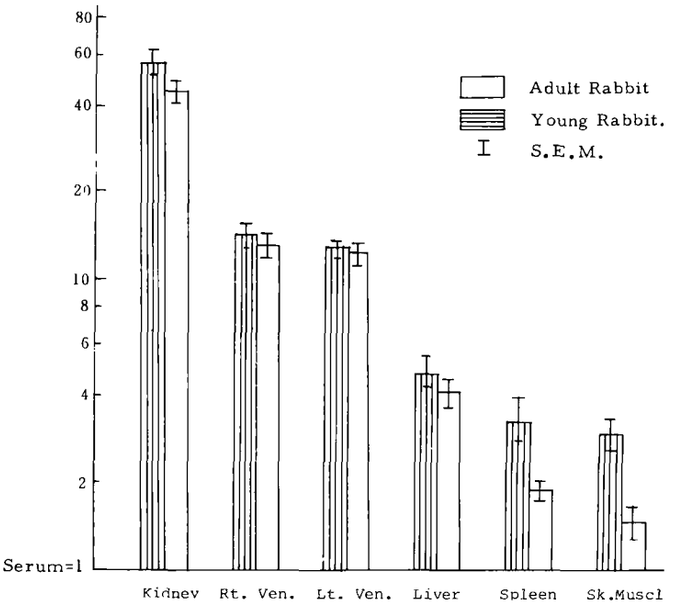


Fig. 4. Ouabain tissue/serum ratio at 240 min after a dose of 0.05 mg/kg. The ratio of the ouabain tissue concentration is plotted vertically on a semilogarithmic scale, the serum concentration be represented as 1.*; $0.01<p<0.025$

constants were nearly same in both age group (Adult rabbits, 0.019 ± 0.003 min^{-1}; Young rabbits, 0.020 ± 0.002 min^{-1}). Young rabbits revealed a significantly larger volume of distribution and greater systemic clearance than adult rabbits. This would indicate nearly the same serum half-life in both age groups.

3. Tissue ouabain concentrations:

Tissue ouabain concentration at 240 minutes after 0.05 mg per kilogram dose of ouabain was highest in the kidney among the tissues sampled (Table 4 and Fig. 4). Ouabain concentration was always significantly higher in adult as compared to young tissues sampled, with the exception of spleen and skeletal muscle. The ratio of the tissue versus serum ouabain concentrations in all tissue except skeletal muscle did not show any difference between adult and young rabbits. The fact that the skeletal muscle ratios were different between young and adult rabbits indicates that skeletal muscle ouabain uptake does not simply follow serum ouabain level.

DISCUSSION

We found that serum ouabain concentration fell with time constants of 5 and 250 minutes in rabbits. Selden and Smith (1972) described in dogs a 4 minute fast phase, followed by a 6 hour period of decreasing rate of concentration decline after

Table 3. Clearances for ouabain in rabbit

(Mean±S.E)

Parameters	Adult Rabbit(n=4)	Young rabbit(n=4)
Systemic Clearance	4.67±0.80 ml/kg/min	9.18±0.74 ml/kg/min*
Renal Clearance	2.83±0.33 ml/kg/min	4.82±0.77 ml/kg/min
Non-renal Clearance	1.87±0.47 ml/kg/min	4.36±0.24 ml/kg/min*

*$p<0.01$, comparing adult with young rabbit values.

Table 4. Tissue cuabain concentration at 240 min after a dose of 0.05 mg/kg

Tissue	Tissue Ouabain Concentration (μg/g)		
	Adult Rabbit(n=6)	Young Rabbit (n=5)	p Value
Left Ventricle	196.47±12.21	104.07±13.92	$p<0.005$
Right Ventricle	209.58±16.06	113.74±18.46	$p<0.005$
Liver	61.91± 4.88	37.16± 4.90	$p<0.01$
Kideny	725.00±51.25	442.81±43.79	$p<0.005$
Spleen	28.71± 4.88	24.38± 3.26	N.S.
Skeletal Muscle	22.55± 2.53	22.09± 1.85	N.S.

Results are expressed as Mean±S.E. Numbers in parentheses indicate the number of tissue samples.
P values are comparisons of adult vs. young rabbit concentrations.

which a very slow exponential phase dominated. However, Marks et al. (1963) reported that the characteristics of distribution and elimination of ouabain were quite different among experimental animals. The addition of a third compartment to the two compartment model would add another exponential term to the serum concentration vs time curve and improve the fit of observed to expected serum concentration values. We adopted our data to the three-compartment model, but could not find a slower exponential phase than those already observed. In addition, it should be emphasized that about 40% of administered ouabain dose was excreted in urine during the 240 minute experimental period. Billiary excretion of ouabain would be high in rabbits. The above results do not suggest any slower elimination phase in rabbits.

Our study indicates that the greater physiological fluid spaces per kilogram of body weight in young animals lead to a large volume of distribution of ouabain. Human as well as canine body fluid spaces per kilogram decline from birth through adulthood (Glantz et al. 1976; Hanna 1963; Young et al. 1963). Systemic ouabain clearances based on kilogram body weight in young rabbits were significantly higher than those of adult animals, but those values were proportional to volume of the central compartment. Proportional changes in these pharmacokinetic parameters account for the similar serum ouabain half-life in both age groups. The larger volume of distribution of ouabain, but similar serum half-life, produces lower serum ouabain concentrations, lower myocardial tissue levels and, therefore, less toxicity. The fact that, clinically, children require larger digoxin doses per kilogram of body weight than do adults to obtain the same steady-state blood levels (Iliaso et al. 1973; Cree et al. 1973), despite no differences in elimination rate, also suggests that the volume of distribution and systemic clearance are larger in children than those in adults.

Other factors besides age-related changes in the pharmacokinetics of digitalis also affect digitalis toxicity. Some workers have reported that immature humans and animals tolerate high serum levels without toxicity (Iliaso et al. 1973; Marsh et al. 1981) and Purkinje fiber from young dogs are less sensitive to the same concentration of ouabain than those from adults (Rosen et al. 1975). Therefore the reason children tolerate higher serum digitalis

levels than adults without becoming toxic remains unclear. Our study could not address itself to this question.

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= 국문초록 =

Ouabain 약력학적 성질의 연령에 따른 변화

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소아 및 미성숙 동물의 digitalis 강심배당체에 대한 tolerance 기전을 추구하기 위한 일환으로 반감기가 짧은 강심배당체인 ouabain을 사용하여 가토에서 성숙도에 따른 약력학적 차이를 분석하여 다음과 같은 결론을 얻었다.

1. Ouabain 정맥투여후 성숙 및 미성숙가토의 혈청농도는 신속한 phase와 느린 phase의 biexponential한 감소양상을 보였다.

2. 체중당 0.05 mg ouabain 투여후 전 실험기간동안 성숙 가토에서 미성숙 가토에 비해 유의하게 약 2배의 높은 혈청 ouabain 농도를 나타내었다.

3. Ouabain의 약력학적 parameter는 ouabain 분포 용적과 clearance 만이 성숙도에 따른 유의한 차이를 보였으며 다른 운반상수 및 시간상수는 차이를 인지할 수 없었다.

4. Ouabain의 뇨중 배설분획은 성숙도에 따른 차이를 보이지 않았다.

5. Ouabain 투여후 240분 후의 조직농도는 신장, 좌우심실근, 간장 조직에서 성숙가토에서 유의하게 높았으나, 조직/혈청 비율은 차이가 없었으며, 조직/혈청 비율은 대퇴부근육 ouabain의 농도만이 성숙도에 따른 차이를 보였다.

이상에서 혈청 ouabain 농도의 성숙도에 따른 차이는 ouabain분포용적과 clearance의 차이에 따른 결과로 추정하였으며, 성숙도에 따른 ouabain의 약력학적 차이는 성숙도에 따른 digitalis 강심배당체에 대한 tolerance차이의 기전으로 관여할 것으로 사료되었다.