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From the Department of Pharmacology and Toxicology, Royal Veterinary and Agricultural University, Copenhagen, Denmark.

PHARMACOKINETICS OF HEXOBARBITAL, SULPHADIMIDINE AND CHLORAMPHENICOL IN NEONATAL AND YOUNG PIGS

By

Ove Svendsen

SVENDSEN, OVE: *Pharmacokinetics of hexobarbital, sulphadimidine and chloramphenicol in neonatal and young pigs.* Acta vet. scand. 1976, *17*, 1—14. — Half-life and apparent specific volume of distribution of hexobarbital, sulphadimidine and chloramphenicol were investigated in newborn, 1, 3, 5 and 8 weeks old pigs. Hexobarbital sleeping time and plasma concentration of hexobarbital at recovery were measured in the same age groups. The half-life of hexobarbital and chloramphenicol was long in newborn pigs but decreased fast during the first week after birth. From 1 to 8 weeks after birth the decrease was less pronounced. The half-life of sulphadimidine increased during the first 3 weeks of life, but in 1 and 3 weeks old pigs the amount of N^4-acetylated sulphadimidine in plasma at 200 min. after the injection was higher than in the newborn pigs.

The apparent specific volume of distribution of hexobarbital, sulphadimidine and chloramphenicol was changed in different ways from birth to 8 weeks of age.

The hexobarbital sleeping time was very long in the newborn pigs and decreased until 3 weeks of age. The concentration of hexobarbital in plasma at recovery was unchanged from birth to 8 weeks of age.

The concentration of chloramphenicol metabolites in plasma 100 min. after the injection increased very fast during the 8 weeks of observation. The concentration of N^4-acetylated sulphadimidine in plasma at 200 min. after the injection increased from birth to 1 week of age, then it decreased.

The data are stressing that the neonatal pig is a convenient model for pharmacokinetic testing of drugs used as pharmacotherapeutics in neonatal life.

pharmacokinetics; hexobarbital; sulphadimidine; chloramphenicol; neonatal pigs.

It has long been known that neonatal and adult mammals differ in their response to different drugs. Several reviews dealing with this subject have been published in recent years (*Nyhan* 1961, *Done* 1966, *Yaffe* 1966, *Mirkin* 1970, *Fouts* 1973).

The most obvious reason for this difference is the low level of drug metabolizing enzyme activity in the liver of neonatal animals as first reported by *Jondorf et al.* (1958) and *Fouts & Adamson* (1959) using microsomes from fetal and newborn laboratory animals. Since these early works the activity of microsomal drug metabolizing enzyme systems has been widely investigated (*Basu et al.* 1971, *Henderson* 1971, *Fouts* 1973, *Rane et al.* 1973), and as a rule the activities are low in neonatals and generally increasing to adult level during the first 3 to 5 weeks after birth.

Donald & Raventós (1939) found that the hexobarbital sleeping time in neonatal pigs is decreasing with age and reaching the adult level about 3 weeks from birth. Low levels of hepatic microsomal drug metabolism in neonatal pigs have been reported by *Short & Davis* (1970) and *Short & Stith* (1973).

Pharmacokinetics of several drugs have been studied in neonatal infants (*Fichter & Curtis* 1956, *Gladtke & Rind* 1965, *Sereni et al.* 1965, 1968, *Krauer et al.* 1968, *Simon et al.* 1972). Generally these studies showed long elimination half-lives of the drugs due to immaturity of the hepatic metabolism and renal excretion. Such studies are difficult to carry out in traditional laboratory animals. Therefore, neonatal and young pigs were chosen in the present investigation of pharmacokinetic parameters of 3 drugs.

MATERIALS AND METHODS

Animals

Neonatal and young pigs (Danish landrace breed) were obtained from a local breeder. The sows were fed barley enriched with 5 l acidified milk until five weeks after delivery, and afterwards the fodder was added a protein-mixture (180—200 g per day) containing soya meal, meat- and bone meal, fish meal, vitamins and mineral salt. The neonatal pigs got milk only from the sow until 3 weeks of age. From this time they got creep feeding consisting of barley, oats, wheat, soya meal, skim-milk powder, fish meal, dried yeast, vitamins and mineral salt ad libitum.

For the study of plasma half-life newborn, 1, 3, 5 and 8 weeks

old pigs were used. The half-lives are calculated as the average of the results from at least 4 pigs (2 females and 2 males).

Half-life and apparent specific volume of distribution

Hexobarbital (enhexymalum NFN), sulphadimidine (sulfadimidinum NFN) and chloramphenicol (chloramphenicolum NFN) were administered intravenously. The dose of chloramphenicol was 50 mg/kg b.wt. as a 10 % (w/v) solution in propylene glycol. The dose of hexobarbital and sulphadimidine was 30 and 100 mg/kg b.wt., respectively, and both were aqueous solutions at 6 and 20 % (w/v), respectively.

The compounds except chloramphenicol were dissolved just before use. The chloramphenicol was dissolved the day before use.

In newborn and 1 week old pigs the intravenous administration was done through the bijugular trunc near the thoracal aperture with the pigs fixed in dorsal recumbency, while the intravenous administration in 3, 5 and 8 weeks old pigs was performed through an ear vein. Blood samples (3—5 ml) were collected ½, 1, 2, 3, 4, 5 and 6 hrs. after the injection except in newborn pigs, where samples were collected ½, 1, 2, 4 and 6 hrs. after the injection. For the estimation of half-life of hexobarbital and chloramphenicol in 5 and 8 weeks old pigs blood samples were also taken ¾ and 1½ hrs. after the injection.

The concentrations of hexobarbital in plasma were estimated by the method of *Cooper & Brodie* (1955). The method described by *Bratton & Marshall* (1939) was used for the estimation of concentrations of free sulphadimidine. The concentration of total sulphadimidine was determined on the same samples after hydrolysis with HCl. The concentration of N^4-acetylated sulphadimidine was calculated as the difference between the concentration of total and that of free sulphadimidine.

The concentrations of biologically active chloramphenicol were determined according to the method of *Kakemi et al.* (1962) modified by *Hughes & Diamond* (1964) while total chloramphenicol (free chloramphenicol plus metabolites with an aromatic nitro group) was measured by the method of *Bessman & Stevens* (1950). The method for the estimation of sulphadimidine and the method of *Bessman & Stevens* had to be modified, because the proteins in plasma from newborn and 1 week old pigs could

not be sufficiently precipitated. The modification of the former method comprised addition of 0.8 ml 5 % bovine albumine solution prior to precipitation. The modification of the method of *Bessman & Stevens* comprised protein precipitation according to the method of *Glazko* (1967) after addition of 3 ml 5 % bovine albumine solution. For the reduction of the aromatic nitro group in chloramphenicol 190 mg zinc powder was used.

The concentrations of the drugs found in plasma were plotted against time in a semilogarithmic coordinate system. From the slope of the linear regression lines through these points the plasma half-life was calculated.

From each half-life curve the concentration of free sulphadimidine and biologically active chloramphenicol was calculated at 200 and 100 min., respectively. The concentration of total sulphadimidine and total chloramphenicol was at the same time calculated by extrapolating the concentrations estimated from the blood samples taken before and after the time of interest.

The apparent specific volume of distribution per kg b.wt. was determined according to *Butler* (1971) from the formula

$$V'd = \frac{Q}{C} \times 100$$

where Q is the dose injected in mg/kg b.wt. and C is the extrapolated zero time concentration in µg/ml plasma and is given in per cent of body weight.

Sleeping time

The pigs receiving hexobarbital fell asleep and the sleeping time was measured. Sleeping time was defined as the time in minutes from the injection until the pigs could stand (*Donald & Raventós* 1939). From the half-life curves the concentrations of hexobarbital in plasma at the end of sleeping time were calculated.

Statistics

The statistical calculations were made in accordance to standard methods (*Kemp* 1955) and the results are given as average ± s.e.m.

RESULTS

Hexobarbital

The disappearance of hexobarbital follows first-order kinetics during the observation period from 30 min. to 6 hrs. A very fast decrease of the plasma half-life during the first week of life is illustrated in Table 1. The half-life decreased further from 1 to 3 weeks of age and was after that unchanged.

Table 1. Effect of age on plasma half-life of hexobarbital, sulphadimidine and chloramphenicol.

Age of pigs	Plasma half-life		
	hexobarbital	sulphadimidine	chloramphenicol
newborn	301[a] ± 24 (4)	775 ± 35 (5)	368[a] ± 27 (5)
1 week	148 ± 16 (4)	787 ± 13 (8)	141[a] ± 9 (10)
3 weeks	113 ± 8 (11)	944 ± 100 (5)	74[b] ± 8 (6)
5 weeks	118 ± 22 (6)	766 ± 73 (8)	63 ± 7 (4)
8 weeks	103[c] ± 11 (5)	548[a] ± 39 (8)	49[b] ± 4 (9)

The values are in minutes ± s.e.m. In brackets the number of pigs.

[a] The value is significantly different ($P < 0.05$) from all other age groups.

[b] The value is significantly different ($P < 0.05$) from all other age groups except the 5 weeks old group.

[c] The value is significantly different ($P < 0.05$) from the 1 week old group.

The average sleeping time (Table 3) is very long in the newborn pigs and decreases fast during the first 3 weeks of life, particularly during the first week. From 3 to 8 weeks of age no further decrease is observed. The calculated mean concentration of hexobarbital in plasma at the end of sleeping time (Table 3) is a little higher in 1 week old pigs than in the other groups of age.

The effect of age on the mean apparent specific volume of distribution is illustrated in Table 2. The volume increases significantly ($P < 0.05$) during the first 3 weeks of age.

Table 2. Effect of age on the apparent specific volume of distribution for hexobarbital, sulphadimidine and chloramphenicol.

Age of pigs	Apparent specific volume of distribution		
	hexobarbital	sulphadimidine	chloramphenicol
newborn	140.4[a] ± 10.0 (4)	80.4[c] ± 0.9 (5)	128.5[e] ± 2.1 (5)
1 week	126.2[b] ± 11.6 (4)	71.3[c] ± 0.9 (8)	156.1[e] ± 6.0 (12)
3 weeks	171.1[a,b] ± 6.6 (10)	51.5[d] ± 0.7 (5)	139.7[f] ± 4.1 (6)
5 weeks	150.1 ± 11.7 (6)	51.5[d] ± 0.7 (8)	145.8 ± 15.1 (4)
8 weeks	161.0 ± 9.5 (5)	64.1[c] ± 1.1 (8)	138.1[f] ± 8.1 (9)

The values are in per cent of body weight ± s.e.m. In brackets the number of pigs.

[a] The values are significantly different ($P < 0.05$).

[b] The values are significantly different ($P < 0.05$).

[c] The value is significantly different ($P < 0.05$) from all other age groups.

[d] The values are equal but significantly different ($P < 0.05$) from all other age groups.

[e] The values are significantly different ($P < 0.05$).

[f] The values are significantly different ($P < 0.05$) from the 1 week old group.

Sulphadimidine

The elimination of sulphadimidine also follows first-order kinetics throughout the entire period being studied.

From Table 1 it can be seen that the plasma half-life tends to increase from birth until 3 weeks of age and then to decrease to values below that of newborn. Only in the 8 weeks old pigs the half-life is significantly ($P < 0.05$) lower than half-lives in the other groups of age.

The apparent specific volume of distribution (Table 2) is high in the newborn and decreases fast during the first 3 weeks of life. Then it increases from 5 to 8 weeks of age. All these differences are statistically significant ($P < 0.05$).

Table 3. Effect of age on the duration of hexobarbital sleeping time and plasma concentration of hexobarbital at the time of recovery.

Age of pigs	Hexobarbital sleeping time*	Plasma concentration of hexobarbital at recovery**
newborn	219[a] ± 4 (4)	16.5 ± 0.9 (4)
1 week	56[a] ± 8 (8)	18.4 ± 1.6 (4)
3 weeks	36 ± 6 (11)	15.2 ± 1.0 (6)
5 weeks	31 ± 4 (6)	17.8 ± 1.3 (6)
8 weeks	30 ± 1 (5)	15.8 ± 0.8 (5)

* The values are in minutes ± s.e.m.
** The values are in μg per ml ± s.e.m.
In brackets the number of pigs.
[a] The value is significantly different ($P < 0.05$) from all other age groups.

Table 4 shows the calculated percentage of N^4-acetylated sulphadimidine in plasma at 200 min. after the injection, and it can be seen that the values vary from 13.5 to 19.6.

Chloramphenicol

The elimination of chloramphenicol follows first-order kinetics during the observation period. Plasma disappearance of injected chloramphenicol is slowest in the newborns and increases fast until 8 weeks of life (Table 1).

The apparent specific volume of distribution (Table 2) is high and it is increasing during the first week of life and then decreasing until 3 weeks of age. From this time the volume is unchanged with age and similar to that of newborns.

Table 4 shows the calculated percentage of chloramphenicol metabolites in plasma at 100 min. after the injection, and it is seen that the values are increasing very fast during the whole observation period, particularly during the first week of life and from third to fifth week of age.

Table 4. Effect of age on the concentration in plasma of N^4-acetylated sulphadimidine at 200 and chloramphenicol metabolites at 100 min. after the injection.

Age of pigs	N^4-acetylated sulphadimidine	Chloramphenicol metabolites
newborn	13.5 ± 1.3 (5)	17.9[c] ± 3.7 (5)
1 week	19.6[a] ± 1.3 (8)	43.5[d] ± 3.4 (12)
3 weeks	17.8[a] ± 0.6 (5)	49.9[d] ± 5.4 (6)
5 weeks	15.1[b] ± 0.6 (8)	70.6[e] ± 5.6 (4)
8 weeks	14.8[b] ± 1.2 (8)	78.2[e] ± 1.6 (9)

The values are concentration of metabolites in per cent of total drug ± s.e.m. In brackets the number of pigs.

[a] The value is significantly different ($P < 0.05$) from the newborn group.

[b] The value is significantly different ($P < 0.05$) from the 1 week old group.

[c] The value is significantly different ($P < 0.05$) from all other age groups.

[d] The values are equal but significantly different ($P < 0.05$) from all other age groups.

[e] The values are equal but significantly different ($P < 0.05$) from all other age groups.

DISCUSSION

Half-life of hexobarbital and chloramphenicol is decreasing during the first 8 weeks of life. Decrease in half-life similar to that found in this study has been reported for several drugs both in animals and humans. e.g. tetracycline derivatives (*Sereni et al.* 1965), sulfisoxazol, sulfamoxole, sulfamethoxine and sulfamethoxypyrazine (*Gladtke & Rind* 1965, *Krauer et al.* 1968, *Sereni et al.* 1968), chloramphenicol (*Nishimura* 1967), penicillins (*Ingall & Klein* 1967, *Simon et al.* 1972), trimethoprim (*Schulz* 1972, *Rasmussen* 1973), and salicylate (*Davis et al.* 1973).

The decrease in half-life during the neonatal period can mainly be explained by increase in hepatic drug metabolism

(*Fouts* 1968, 1973, *Rane et al.* 1973) and renal excretion *Barnett & Vesterdal* 1953, *Horster & Lewy* 1970).

In contrast to the renal excretory capability the hepatic drug metabolism has been studied in neonatal and young pigs by *Short* (1969), *Short & Davis* (1970) and *Short & Stith* (1973) and according to their findings the development of hepatic microsomal drug metabolizing enzyme activity reached maximum level at the age of 3 to 6 weeks.

Pharmacokinetic parameters of drugs are influenced by plasma protein binding capacity and volumes of body fluid compartments. Plasma protein binding capacity has been reported to be low in neonatal humans (*Ganshorn & Kurz* 1968, *Chignell et al.* 1971, *Ehrnebo et al.* 1971, *Pruitt & Dayton* 1971) and in newborn pigs (*Svendsen et al.* 1972, *Short & Tumbleson* 1973). Thus the amount of unbound freely diffusable chloramphenicol in plasma of newborn infants is 1.4 to 2.0 times higher than the values in adult humans (*Ganshorn & Kurz*). Both the total body water and extracellular fluid compartments have been shown to decrease with age in the beagle dog (*Sheng & Huggins* 1972).

The decrease in hexobarbital sleeping time followed the decrease in hexobarbital half-life, and the concentration of hexobarbital in plasma at recovery was unchanged with age. These findings support that the age related decrease in half-life and sleeping time is influenced by increase in hexobarbital metabolism.

Hexobarbital is concentrated in the fat of the body, and the establishment of diffusion equilibrium with the fat depots takes several hours. According to *Manners & McCrea* (1963) and *Brooks & Davis* (1969) the percentage of fat in the body of newborn pigs is 1.2 % and in 4 weeks old pigs 17.8 %. This age related difference in fat content easily explains the observed increase in the apparent specific volume of distribution of hexobarbital. The age related decrease in hexobarbital half-life and hexobarbital sleeping time of this study might therefore also reflect the increased fat content to the body.

The finding in this study that hexobarbital sleeping time is decreasing fast during the first 3 weeks of age is in agreement with *Donald & Raventós* (1939) using pigs and *Catz & Yaffe* (1967) using mice. *Catz & Yaffe* also demonstrated constant plasma concentration of hexobarbital at the time of awakening in mice of different ages.

The half-life of sulphadimidine tends to increase from birth until 3 weeks of age and is then decreasing significantly and so is the level of sulphadimidine in plasma at zero time. The longer half-life of sulphadimidine in 3 weeks old pigs compared to newborn pigs can not be explained as an effect of decreasing metabolic activity because the amount of N^4-acetylated sulphadimidine is a little higher in 3 weeks old pigs than in newborn pigs.

Chloramphenicol is primarily inactivated by glucuronic acid conjugation and in less amount by hydrolysis, dehalogenation and formation of aryl amines (*Glazko* 1967). All these metabolic products are highly water soluble, particularly the glucuronidation products and this should be kept in mind when evaluating the very high percentage of chloramphenicol metabolites in plasma 100 min. after the injection in 5 and 8 weeks old pigs.

In rats and dogs nearly 80 and 50 % of a dose of chloramphenicol is recovered as metabolites in the bile (*Glazko et al.* 1949, 1952). In newborn rats the biliary excretion capacity is low (*Klaassen* 1972) as is the renal excretory capacity. This suggests that the relatively high percentage of chloramphenicol metabolites in plasma of the newborn pigs at 100 min. after the injection is reflecting more than the metabolic activity compared to the 8 weeks old pigs.

The plasma level of chloramphenicol in newborn infants is found to be higher than the level in children (*Glazko*) which is corresponding with the findings of this study.

The half-life of total chloramphenicol is found to be 1.3 hrs. in adult pigs (*Davis et al.* 1972). This is a little higher than the half-life of active chloramphenicol in the 8 weeks old pigs of this study.

From the present study it has been demonstrated that pharmacokinetic investigations are easily performed in neonatal and young pigs and that neonatal pigs pharmacokinetically are showing age-related changes similar to those of neonatal humans and neonatal animal species. In conclusion it must therefore be stressed that the neonatal pig is a convenient model for pharmacokinetic testing of drugs used as pharmacotherapeutics in neonatal life.

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SAMMENDRAG

Farmakokinetik af enhexymal, sulfadimidin og chloramphenicol hos neonatale og unge grise.

Halveringstiden og fordelingsvolumenet af enhexymal, sulfadimidin og chloramphenicol er undersøgt hos nyfødte, 1, 3, 5 og 8 uger gamle grise. Enhexymal-sovetiden er målt og koncentrationen af enhexymal i plasma ved sovetidens ophør er beregnet hos de samme aldersgrupper.

Halveringstiden af enhexymal og chloramphenicol er meget lang hos nyfødte grise, men den afkortes hurtigt efter fødselen, specielt i løbet af den første leveuge. Halveringstiden af sulfadimidin forlænges i løbet af de første 3 leveuger. To hundrede min. efter injektionen er mængden af N^4-acetyleret sulfadimidin i plasma højere hos 1 og 3 uger gamle grise end hos nyfødte grise.

Fordelingsvolumenet af enhexymal, sulfadimidin og chloramphenicol ændres på forskellig måde i løbet af de første 8 leveuger. Enhexymal-sovetiden er meget lang hos nyfødte grise og falder indtil 3 uger efter fødselen. Koncentrationen af enhexymal i plasma ved sovetidens ophør er uforandret fra fødsel til 8 uger efter fødselen.

Koncentrationen af chloramphenicolmetabolitter i plasma 100 min. efter injektionen stiger stærkt fra fødsel til 8 uger efter fødselen. Koncentrationen af N^4-acetyleret sulfadimidin i plasma 200 min. efter injektionen stiger fra fødsel til første leveuge og falder derefter.

På grundlag af undersøgelsens resultater konkluderes det, at neonatale grise er en anvendelig dyremodel til farmakokinetiske undersøgelser af lægemidler, som anvendes i den neonatale farmakoterapi.

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Reprints may be requested from: Ove Svendsen, Department of Pharmacology and Toxicology, H. Lundbeck & Co. A/S, Ottiliavej 7—9, DK-2500 Copenhagen-Valby, Denmark.