The European Agency for the Evaluation of Medicinal Products
Veterinary Medicines and Information Technology

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COMMITTEE FOR VETERINARY MEDICINAL PRODUCTS

THIOPENTAL SODIUM

SUMMARY REPORT

1. Thiopental sodium [4,6(1H,5H)-pyrimidinedione, 5-ethyldihydro-5-(1-methylbutyl)-2-thioxo-monosodium salt, synonym: thiopentone sodium] is an intravenous thiobarbiturate anaesthetic used in humans and animals. It is classified as a short-acting barbiturate. It has a brief duration of effect and is used in short procedures such as setting fractures and for radiographic and other examinations. It may also be used to induce anaesthesia.

2. Thiopental sodium is used clinically in several animal species including swine, cattle, horses, goats, birds and rabbits. It is administered only as a single intravenous injection. Doses in the range 5.5 to 22 mg/kg bw are recommended for pigs, cattle, horses and goats, 30 to 50 mg/kg bw for rabbits, 13 to 22 mg/kg bw for geese, 18 to 26 mg/kg bw for ducks and 13 to 18 mg/kg bw for chickens and pigeons.

3. Thiopental depresses the activity of the cortex of the brain, both motor and sensor areas. Relatively large dosages are necessary to completely abolish the perception of pain. Thiopental depresses the respiratory centre at considerably smaller concentration than is needed for cardiac arrest. Subanaesthetic doses accelerate the respiratory rate. Thiopental induces tachycardia, and the incidence of ventricular fibrillation is increased.

4. In normal humans, an intravenous dose of 4 to 5 mg/kg bw is needed for induction. A higher dose of 6 to 8 mg/kg bw may be needed in children and a lower dose of 2 to 2.5 mg/kg bw in the elderly. The plasma concentration needed for anaesthesia is 40 µg/l, corresponding to a free plasma concentration of around 6 µg/l. An intravenous dose level of 1 mg/kg bw was reported to be a sub-anaesthetic dose in humans. Based on limited pharmacological data provided no pharmacological NOEL can be established in humans.

5. In humans, the pharmacokinetics and plasma binding of thiopental have been studied in women submitted to Caesarean sections (doses not identified). Mean serum values (± SD) for 7 women were: Volume of Distribution (Vd) initially 17.3 ± 8.5 litres/person, apparent Vd 564 ± 343 litres/person, Vd at steady state 288 ± 180 litre/person, systemic plasma clearance 0.286 ± 0.156 l/min/person, rate of change of Vd at zero time 1.03 ± 0.36 l/min/person and $t_{1/2}$ 26.1 ± 12.6 hours. According to this study the differences in maternal distribution and elimination characteristics of thiopental may be more important determinants of intersubject differences in foetal drug exposure than differences in dose or dosing-delivery interval. In other studies, thiopental was shown to be bound to plasma proteins, the amount of binding (50 to 80%) varying with plasma or tissue pH and drug concentration. The substance was initially distributed to the highly perfused tissues, including brain. The subsequent slower redistribution was to lean tissues, with some contribution by fat. The final elimination phase involved metabolism of the drug and redistribution to poorly perfused fat. The distribution half-life was 8.5 minutes in the rapid phase and 63 minutes in the slow phase. Clearance was 3.4 ml/kg/minute. The elimination half-life was in the range 4 to 12 hours (mean 9 hours). Metabolism was mainly by the liver with oxidation of the 1-methyl butyl side chain to a hypnotically inactive substance.

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6. In *in vitro* studies, several tissues have been reported to metabolise thiopental, i.e. liver, kidney, brain, muscle, heart and jejunum and erythrocytes.

7. In female albino rats, after receiving thiopental sodium (1%, 30 mg/kg intravenously during 30 seconds), the tissue/blood ratios during the time of equilibrium were approximately 0.6 for brain (from 1 minute to 2 hours), 2.5 for liver (1 minute to 6 hours) and 7.0 for fat (1 to 22 hours). The rate of metabolism during the first 6 hours was 10% per hour, and at 12 hours 90% of the substance was metabolised.

8. After partial hepatectomy (70% of the liver removed), 27% of thiopental was metabolised in 12 hours (operated controls 82%). After bilateral nephrectomy, 58% was metabolised in 12 hours.

9. In intact mice thiopental was found to be rapidly metabolised. Twenty-four hours after intraperitoneal administration (100 mg/kg bw, 2 animals) no parent compound was detected in the body.

10. Based on *in vitro* organ incubations, in the rabbit thiopental was mainly metabolised in the liver and kidney to the corresponding carboxylic acid.

11. Thiopental sodium given intravenously (20 mg/kg bw) to 20 dogs showed a maximum localisation of the drug in fat in 4 hours. The mobilisation was slightly faster in the rat compared to the dog. In the dog, thiopental was almost completely metabolised, but only traces of the carboxylic acid derivatives were found in the urine. The pharmacokinetics of thiopental sodium were studied in 6 mongrel dogs after an intravenous bolus equivalent to 20 mg/kg bw. The plasma protein binding was quite high (73.8 ± 4.1%). The half-life of the initial phase (distribution/redistribution) was 14.9 ± 3.3 minutes. The apparent volume of distribution was 843 ± 194 ml/kg. The terminal half-life was 6.99 ± 2.18 hours and body clearance was 1.51 ± 0.60 ml/kg x min. The degree of ionisation of thiopental in the pH of plasma is about 39%. Redistribution was found to be responsible for recovery from thiopental anaesthesia.

12. The mechanisms of thiopental metabolism were studied in a monkey injected with 35 mg/kg bw radioactively labelled thiopental sodium. At the end of 4 days 86.2% of all the radioactivity was found in the urine with 14.1% as chloroform extractable material and 17.1% as inorganic sulphate. Paper chromatography indicated the presence of at least 12 metabolites (not identified).

13. A group consisting of 5 horses and one pony and a second group consisting of 6 ponies were sedated. One hour later, anaesthesia was induced with 11 mg/kg bw thiopentone sodium, administered by rapid intravenous injection. Blood samples were collected at intervals and total (free and bound) thiopentone concentrations in plasma were determined using HPLC. The distribution kinetics were best described by a 3-compartment open model. There was an initial rapid distribution of thiopental from plasma, illustrated by the very short half-life (mean value 1.4 minutes for group 1 and 1.3 minutes for group 2). This was followed by a second, comparatively slower, distribution phase with a half-life (mean 15.9 minutes for group 1 and 11.4 minutes for group 2). The terminal elimination half-life was 156 minutes for group 1 and 222 minutes for group 2. In group 1, the pony had the longest elimination half-life. Overall, the elimination half-life was significantly shorter in the horses (mean value 147 minutes) than in the ponies. The wide distribution of thiopentone was shown by the large volume of distribution (783 ml/kg for group 1 and 1127 ml/kg for group 2). There was no significant difference in clearance between the horses (mean value 3.5 ml/min/kg) and ponies (mean value 3.6 ml/min/kg).

14. Sheep were given a single intravenous dose of 20 mg/kg bw thiopental. The mean apparent volume of distribution was 1005 mg/kg, clearance was 3.5 ml/kg/min and the half-life for plasma elimination was 196 minutes.

15. In a comparative study, groups of 6 sheep, 6 rabbits and 6 dogs were given a short intravenous infusion of 8.2, 8.8 and 9.0, mg/kg bw/min, respectively, until early burst suppression was achieved on the electro-encephalogram. The overall dose corresponded to 24.3, 21.6 and 35.9 mg/kg bw for the 3 species, respectively. Following termination of the infusion, plasma concentration-time data decayed in a tri-exponential fashion. The mean terminal plasma elimination half-lives were 252 minutes for sheep, 43 minutes for rabbits and 182 minutes in dogs. The mean residence times in sheep, rabbits and dogs were 344, 47 and 262 minutes, respectively.

16. The LD_{50} values for mice were 58 to 100 mg/kg bw intravenously, 135 to 154 mg/kg bw intraperitoneally, 225 mg/kg bw subcutaneously, 208 to 600 mg/kg bw orally. The LD_{50} values for rats were 44 to 64 mg/kg bw intravenously and 117 mg/kg bw orally. The LD_{50} value for rabbits was 31 mg/kg bw intravenously and for dogs 36 to 50 mg/kg bw intravenously. Death was caused by depression of the respiratory centre. When administered intravenously, the lethal dose varied with the rate of injection.

17. In a repeated-dose toxicity dog study (25 mg thiopental sodium/kg bw intravenously 3 times a week for 30 days) one of the four animals died. The death was considered to be drug-related. No NOEL could be established. The study was not carried out according to Volume VI of the Rules Governing Medicinal Products in the European Community. No oral toxicity studies were provided.

18. There is some information in the literature about hepatotoxicity of thiopental sodium following the administration of large doses to animals. Intravenous administration of 20 mg/kg bw to dogs, twice daily for 2 to 3 weeks resulted in slight depression of liver function. However there are no human clinical data to suggest that the doses used for induction of anaesthesia have a hepatotoxic effect, even in patients with an already damaged liver.

19. Pregnant Potsdam-Rehbrücker strain rats were given thiopental sodium intraperitoneally at a dose of 204 mg/kg bw on day 4 of gestation to 4 rats and 408 mg/kg bw on day 4 of gestation to 2 rats. No evidence for teratogenic potential was found. In a second study, the effect of thiopental sodium upon embryonic development of ICR-JCL mice was investigated. The mice were intraperitoneally injected with thiopental sodium 0, 25, 50, 75, 100 or 150 mg/kg bw on day 11. At 150 mg/kg bw, all dams died and one dam (out of 16) administered 100 mg/kg bw also died. The surviving animals were autopsied on day 18, and their foetuses were examined. Doses of 75 mg/kg bw and above caused an increase in dead foetuses. Doses of 50 mg/kg bw and above caused a significant reduction in foetal body weights and an increase in delayed ossification of the mid-phalanges. There was no evidence of teratogenicity. Neither study was completely satisfactory because dosing was not carried out for the appropriate period of organogenesis.

20. No 2-generation reproduction studies were provided, however, in view of the rapid elimination of the substance and its limited use, these data were not considered necessary.

21. No data on mutagenicity were available, however, in view of the rapid elimination of the substance and its limited use, these data were not considered necessary.

22. No data on carcinogenicity were available and therefore no conclusion on the carcinogenic potential of thiopental sodium can be drawn. However, in view of the rapid elimination of the substance and its limited use, these data were not considered necessary.

23. No data on immunotoxicity were provided. There are some data in the literature about thiopental sodium suppressing white blood cells functions.

24. Thiopental sodium is used as an intravenous anaesthetic in humans for short surgical procedures (like setting fractures) and for induction of anaesthesia prior to inhalation anaesthetics. Adverse reactions to thiopental sodium are listed for the 30 year period from 1963 to 1993, but the information of total number of treatments is lacking. The most frequent adverse reactions in humans seem to be anaphylactic shock and bronchospasms. Incidence rate has not been provided.

25. Due to the limited data submitted, no overall oral toxicological or pharmacological NOEL could be identified and therefore no ADI could be established. Despite this, it was considered that there would be no undue risk to consumers from residues in edible tissues, due to the rapid elimination of the substance in the pharmacokinetic studies.

26. No data concerning residue depletion have been provided. Because the pharmacokinetic data indicated that the substance was rapidly eliminated in all species, it was considered that residues depletion data were not necessary.

27. An analytical method based on HPLC with UV detection was described in the published literature. Carbamazepine was used as an internal standard. The method had been used by several workers to determined residues of thiopental in human and animal plasma and in rat tissues. However, the method had not been validated for the edible tissues of the target species.

Conclusions and recommendation

Having considered the criteria established by the CVMP for the inclusion of substances in Annex II of Council Regulation (EEC) No 2377/90, and in particular that:

- thiopental sodium is used in individual animals, for infrequent or non-regular treatments,
- the substance is rapidly eliminated from the target species after intravenous administration; there were no pharmacokinetic data relating to other routes of administration;

the Committee for Veterinary Medicinal Products concludes that there is no need to establish an MRL for thiopental sodium and recommends its inclusion in Annex II to Council Regulation (EEC) No 2377/90 in accordance with the following table:

Pharmacologically active substance(s)	Animal species	Other provisions
Thiopental sodium	All food producing species	For intravenous administration only