



COMMITTEE FOR VETERINARY MEDICINAL PRODUCTS

GENTAMICIN

SUMMARY REPORT (1)

1. Gentamicin is an aminoglycoside antibiotic indicated for the treatment of a variety of bacterial infections in pigs, cattle, poultry and horses. It is composed of three major components designated C, C₂ and C_{1a}.
2. Gentamicin is poorly absorbed from the gastrointestinal tract. After parenteral doses it distributes into extracellular space but significant amounts penetrate into the kidney cortex and inner ear. There is negligible biotransformation of the drug following parenteral administration and unchanged gentamicin is excreted rapidly in the urine.
3. It has low acute toxicity after oral administration to rodents (LD₅₀ 8000-10000 mg/kg bw) but is more toxic following intravenous (LD₅₀ 37-67 mg/kg bw) and intramuscular (LD₅₀ 200- 890 mg/kg bw) administration, again suggesting poor absorption after oral dosing.
4. The drug has been extensively studied in subchronic toxicity tests, after intramuscular and subcutaneous administration to rats and dogs for periods of up to 12 months. In rats given up to 200 mg/kg bw/day intramuscularly, the kidney was the primary target organ with interstitial nephritis and toxic nephrosis as the main findings. The lowest NOEL from these studies was 25 mg/kg bw/day. After subcutaneous administration for up to 28 days with doses of up to 150 mg/kg bw/day the kidney was again the target organ. Altered renal function was noted at the lowest dose used (50 mg/kg bw/day).
5. In an oral study, rats were fed diets containing gentamicin to maintain doses of up to 116 mg/kg bw/day. The only adverse signs noted were soft stools. The NOEL was 19.4 mg/kg bw/day.
6. In dogs given daily doses of up to 120 mg/kg bw/day for up to 12 weeks, the main effect was renal toxicity. The lowest NOEL was 10 mg/kg bw/day. However, in a one year study where animals were given up to 8 mg/kg bw/day, 5 days per week, no NOEL was identified.
7. Toxicity to the inner ear is a recognised effect of aminoglycoside antibiotics. However, there were no clear indications of ototoxicity in the subchronic studies. A special study in monkeys at doses of up to 50 mg/kg bw/day showed hair cell loss and reduced sensory epithelium in addition to functional hearing loss.
8. A multigeneration study in the rat showed no adverse effects on reproduction after intramuscular injections of 5 and 20 mg/kg bw/day. There was no evidence of teratogenic effects in studies with mice, rats, guinea-pigs and rabbits, but fetotoxicity (fetal death) was seen in mice (10 mg/kg bw/day) and rats (50 mg/kg bw/day).
9. Gentamicin has been tested in a range of genotoxicity studies and most gave negative results. However, positive results were noted in tests for forward mutation in *E. coli*, in a test for chromosome aberrations in mouse L-cells and in a test for sister chromatid exchange in human fibro blasts.
10. No carcinogenicity studies were available.

11. There were no data available on the effect of gentamicin on or human gut flora. However, in vitro data were available on MIC values using over 600 clinical isolates of anaerobic bacteria including some representative of the human gut flora. Many were resistant to gentamicin and the most sensitive species was Eubacterium. MIC values for this species were in the range 0.1-25 µg/ml with an MIC₅₀ of 0.8 µg/ml.
12. In view of the poor absorption of gentamicin from the gastrointestinal tract, it was considered that the most relevant adverse effects were likely to be those on the human intestinal microflora. In developing the provisional microbiological ADI, the following equation and parameters were used:
- the concentration without effect on the human gut flora was 0.8 µg/ml.
 - this was adjusted by a factor of 2 to take into account a relatively low inoculum density .
 - absorption of gentamicin from the gut is low so a factor of 1.0 was used to represent 100% availability to the microflora.
 - 150g for the human fecal bolus.
 - a safety factor of 1.0 to cover variability between individuals.
13. Only low levels of residues were found in pigs given intramuscular or oral doses of ³H-gentamicin as determined by total radioactivity or antimicrobial assay. After intramuscular injection the target tissues were kidney and liver with only low levels being found in muscle or fat. Residues in kidney depleted to below the limit of detection (0.08 mg/kg) by day 14. Similar findings were made in cattle.

In dairy cattle given gentamicin by intramuscular injection, intramammary infusion or intrauterine infusion, milk was free of detectable residues 60-84 hours post-treatment.

No residues data were available in poultry, eggs or horses.

14. As metabolism of the drug is negligible, the parent compound gentamicin was chosen as the marker residue.
15. Based on the temporary ADI of 0-4 µg/kg bw/day and the residues depletion profiles, the following provisional MRLs were elaborated for cattle and pigs:

muscle	100	µg/kg
liver	200	µg/kg
kidney	1000	µg/kg
fat	100	µg/kg
milk	100	µg/l

These MRLs expire on 1 June 2000.

16. There are a number of validated methods of analysis for the determination of gentamicin residues in tissue. One of these uses an HPLC method with limits of quantitation of 100 µg/g for liver and kidney. Methods are available for milk but these lack sensitivity.

LIST OF QUESTIONS

The following list takes into account the questions developed during the 43rd meeting of JECFA and those previously adopted by the CVMP.

Safety file

1. Data about the effects on the human gut flora and micro-organisms used in the food industry are required.
2. NOELs for oto- and nephro-toxicity are required.
3. Information concerning the potential for reproductive toxicity and teratogenicity should be provided. Human epidemiological evidence would be acceptable.
4. A battery of mutagenicity studies conducted in accordance with the requirements of Volume VI of the Rules Governing Medicinal Products in the European Community are required.
5. Information to assist in the assessment of carcinogenic potential, including:
 - the results of genotoxicity assays for gene mutations in mammalian cells and chromosome aberrations in vitro and in vivo.
 - details of an investigation on possible structural similarities between gentamicin and known carcinogens.

Residue file

1. Residues depletion data, in all relevant tissues, including injection sites and species, in accordance with the requirements of Volume VI of the Rules Governing Medicinal Products in the European Community should be provided.
2. A validated analytical method with a limit of quantitation at or below the recommended MRL for milk should be provided.
3. The validated methods of analysis described in the JECFA evaluation must be provided to the CVMP.

This information should be provided to the CVMP by 1 January 2000.