PRODUCT MONOGRAPH

AVA-MINOCYCLINE

Minocycline Hydrochloride Capsules USP

50 mg and 100 mg

Antibiotic

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DATE OF PREPARATION:
February 11, 2011

Control#: 144965

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Minocycline Hydrochloride Capsules USP

50 mg and 100 mg

THERAPEUTIC CLASSIFICATION

Antibiotic

ACTIONS

AVA-MINOCYCLINE (minocycline hydrochloride) is a tetracycline with antibacterial activity against some Gram-negative and Gram-positive organisms. The action of AVA-MINOCYCLINE is primarily bacteriostatic and is thought to exert its antimicrobial effect by the inhibition of protein synthesis.

Comparative Bioavailability

A single-dose, standard two-way crossover bioavailability study was performed using normal human volunteers. The rate and extent of absorption of minocycline after a single oral dose of 200 mg given as either two 100 mg MINOCIN capsules or as two 100 mg AVA-MINOCYCLINE capsules was measured and compared. The results are summarized as follows:

	AVA-MINOCYCLINE	MINOCIN	PERCENTAGE OF MINOCIN
AUC_T* (μg · hr/mL)	62.08 (22)	62.79 (16)	-1.1
AUC_I* (μg · hr/mL)	66.56 (23)	66.99 (17)	-0.6
Cmax* (μg · mL)	3.52 (18)	3.49 (17)	+0.9
Tmax** (hr)	2.35 (0.71)	2.28 (0.83)	+3.1
t1/2** (hr)	18.62 (3.39)	18.11 (3.02)	+2.8

* Geometric means (CV)
** Arithmetic means (SD)

INDICATION AND CLINICAL USES

AVA-MINOCYCLINE (minocycline hydrochloride) may be indicated for the treatment of the following infections due to susceptible strains of the designated organisms:

Gallbladder infections caused by Escherichia coli;

Urinary tract infections: cystitis, gonorrhea, pyelonephritis caused by Escherichia coli, Proteus species, Klebsiella species, Enterobacter aerogenes, Neisseria gonorrhoeae.

When penicillin is contraindicated, minocycline may be employed as an alternative drug in the treatment of anal and pharyngeal gonorrhea and syphilis.

Skin and soft tissue infections: abscess cellulitis, furunculosis, impetigo and pyoderma caused by: Staphylococcus epidermidis, Staphylococcus aureus, Streptococcus pyogenes, Proteus species, Escherichia coli.

Although tetracyclines are not the drugs of choice in any staphylococcal or streptococcal infection, minocycline could be useful in circumstances where these organisms are shown to be resistant to other agents but sensitive to minocycline. Bacterial evaluation of clinical cases involving proteus suggests a relatively lower success rate may be expected where these organisms are concerned.

Respiratory tract infections: bronchitis, pharyngitis, pneumonia, bronchopneumonia, sinusitis and tonsillitis caused by: Haemophilus influenzae, Klebsiella species, Enterobacter species. Tetracyclines should not be prescribed for acute throat infections.

CONTRAINDICATIONS

History of hypersensitivity to minocycline or any other tetracycline. .

WARNINGS

Newborns, Infants and Children:

The use of tetracyclines, including minocycline, during tooth development (last half of pregnancy, infancy and childhood under the age of thirteen years) has been shown to cause permanent tooth discolouration (yellow-grey-brown) . This is more common during long-term use, but has been observed following short-term courses. Enamel hypoplasia has also been reported. All tetracyclines including minocycline form a stable calcium complex in any bone-forming tissue. A decrease in the fibula growth rate has been observed in prematures given oral tetracycline in doses of 25 mg/kg every 6 hours. This appeared to be reversible when the drug was discontinued. Minocycline should not be used in such patients unless other drugs are ineffective or are contraindicated.

Pregnancy and Lactation:

Tetracyclines, including minocycline, are not recommended during pregnancy and lactation because of possible adverse effects on developing bones and teeth of the fetus and neonate. Results of animal studies indicate that tetracyclines cross the placenta, are found in fetal tissues and can have toxic effects on the developing fetus (often related t o retardation of skeletal development). Evidence of embryo-toxicity has also been noted in animals treated early in pregnancy. The safety of minocycline for use during pregnancy has not been established.

Tetracyclines, including minocycline, are excreted in the milk of lactating women.

It is advisable to avoid giving minocycline in conjunction with penicillin since some bacteriostatic drugs may interfere with the bactericidal action of penicillin .

Minocycline should not be used for the treatment of streptococcal diseases unless the organism is demonstrated to be sensitive, since most streptococci have been found to be resistant to tetracycline drugs. If it is deemed necessary that infection due to Group A beta-hemolytic streptococci be treated with minocycline, then such treatment should be continued for at least ten days.

In the presence of significant renal impairment, usual oral doses may lead to excessive systemic accumulations of minocycline and possible liver toxicity. Under such conditions, lower than usual doses may be indicated. After initial therapy, and if therapy is prolonged, serum level determinations of the drug are advisable.

The anti-anabolic action of tetracyclines can also produce dose-related increases in BUN; consequently, in patients with significant renal impairment, elevated serum minocycline levels can lead to azotemia, hypophosphaternia and acidosis.

Minocycline is capable of aggravating the symptoms associated with lupus erythematosus. Therefore, caution should be taken when administering the drug to patients with this disease.

Minocycline has been shown to depress plasma prothrombin activity. Therefore patients who are on anticoagulant therapy should be monitored regularly and may require downward adjustment of their anticoagulant dosage. Interference with vitamin K synthesis by micro-organisms in the gut has been reported.

Cross-sensitization among the various tetracyclines is extremely common.

Pigmentation of skin, thyroid, bone and teeth have been reported occasionally in persons receiving minocycline usually for extended periods of time. The pigmentation may be irreversible.

PRECAUTIONS

The administration of AVA-MINOCYCLINE (minocycline hydrochloride) to children under 13 years of age is not recommended.

Bulging fontanels have been reported in young infants following full therapeutic dosage of tetracyclines including minocycline. Pseudotumor cerebri has very rarely been reported in adults. These signs disappeared rapidly when the drug was discontinued.

Patients should be warned to avoid exposure to direct sunlight and/or ultraviolet light while under treatment with minocycline or other tetracycline drugs, and treatment should be discontinued at the first evidence of skin erythema or discomfort. Photosensitivity manifested by an exaggerated sunburn reaction has been observed in some individuals taking tetracyclines. Studies to date indicated that photosensitivity is rarely reported with minocycline.

Patients treated with minocycline may suffer from headaches, light-headedness, dizziness or vertigo. Administration of minocycline in excess of the recommended dosage can increase the frequency and severity of these CNS symptoms. Patients should be cautioned about driving vehicles or using hazardous machinery while on minocycline therapy. These symptoms may disappear during therapy and usually disappear rapidly when the drug is discontinued.

As with other antibiotics, minocycline therapy may result in overgrowth of non-susceptible organisms (including fungi). If superinfection occurs, minocycline should be discontinued and appropriate therapy instituted.

The development of cross-resistance to many antibiotics can develop rapidly in several species of microorganisms. The clinician should bear this in mind if therapy with minocycline is not achieving expected results.

The frequency of resistance to minocycline in hemolytic streptococci is highest in strains from infections of the ear, wounds and skin. Culture and sensitivity studies should be performed whenever feasible and routinely in suspected streptococcal infections.

Since sensitivity reactions are more likely to occur in persons with a history of allergy, asthma, hay fever, or urticaria, minocycline should be used with caution in such individuals.

Before treating patients with gonorrhea, a darkfield examination should be made from any lesion suggestive of concurrent syphilis. Serological tests for syphilis should be repeated monthly for at least 4 months.

Minocycline should be used with caution in patients with hepatic dysfunction and in conjunction with alcohol or other hepatotoxic drugs.

In long-term therapy with minocycline, periodic laboratory evaluation of organ systems, including hematopoietic, renal and hepatic studies should be performed.

Minocycline has been shown to depress plasma prothrombin activity. Therefore, patients who are on anticoagulant therapy should be monitored regularly and may require downward adjustment of their anticoagulant dosage. Interference with vitamin K synthesis by microorganisms in the gut has been reported.

Antacids containing aluminum, calcium or magnesium and oral iron preparations impair absorption and should not be given to patients taking oral minocycline.

Dairy products can delay absorption. Studies to date have indicated that the absorption of minocycline is not notably influenced by foods.

ADVERSE REACTIONS

The following adverse reactions have been reported with the tetracycline analogues including minocycline:

(a) Central Nervous System: increased intracranial pressure, headaches, light-headedness, dizziness or vertigo and, rarely, fainting spells have been reported with a variable but overall incidence of approximately 7% in patients treated with minocycline. These symptoms usually disappear rapidly when the drug is discontinued.

(b) Gastrointestinal System: anorexia, nausea, vomiting, diarrhea, stomatitis, glossitis, enterocolitis, pruritis ani, constipation, dysphagia and inflammatory lesions (with monilial overgrowth) in the anogenital region.

(c) Teeth and Bone: dental staining (yellow-gray-brown) has been reported in children of mothers given tetracyclines, including minocycline, during the latter half of pregnancy, and in children given the drug during the neonatal period, infancy and childhood to age of 13 years. Enamel hypoplasia has also been reported. Discolouration of bones and teeth has been documented to occur rarely in adolescents and adults upon extended treatment with minocycline. The effects may be irreversible. At present the mechanism of staining, although not completely elucidated, appears to be mediated by the formation of a stable iron complex.

(d) Renal: rise in BUN has been reported and is apparently dose-related. Increased excretion of nitrogen and sodium has also been reported.

(e) Skin: maculopapular and erythematous rashes. Rarely reported - exfoliative dermatitis, onycholysis, discolouration of the nails, pigmentation of the skin and mucous membrane, erythema multiforme, Stevens-Johnson syndrome.

(f) Hypersensitivity reactions: urticaria, angioneurotic edema, anaphylaxis, anaphylactoid purpura, pericarditis and exacerbation of systemic lupus erythematosus.

(g) Other: elevated SGOT or SGPT values, hepatic cholestasis, hemolytic anemia, neutropenia, thrombocytopenia and eosinophilia. When given over prolonged periods, minocycline, like other tetracyclines, has been reported to produce brown-black microscopic discolouration of the

thyroid gland. Abnormalities of thyroid function have not been shown to date. If adverse reactions or idiosyncrasy occur, the administration of minocycline should be discontinued and appropriate alternate therapy instituted.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

Symptoms and Signs:

Dizziness, nausea, vomiting, abdominal pain, intestinal hemorrhage, hypotension, lethargy, coma, acidosis, azotemia without a concomitant rise in creatinine.

Treatment:

Specific antidote: none.

General antidotes: Antacids (e.g., calcium carbonate or lactate, milk of magnesia, aluminium hydroxide) which form relatively insoluble complexes with minocycline. (Calcium Solution 5%: 50 g calcium carbonate or lactate dissolved in 1000 mL water, yields a 5% solution). Gastric lavage, if necessary.

DOSAGE AND ADMINISTRATION

Children 13 Years of Age or Older:

The usual dosage of AVA-MINOCYCLINE (minocycline hydrochloride) is 4 mg/kg initially followed by 2 mg/kg every 12 hours. Tetracyclines are not recommended in children under 13 years of age (see WARNINGS).

Adults:

The usual oral dosage of AVA-MINOCYCLINE is 100 mg or 200 mg initially, followed by 100 mg every 12 hours. Alternatively, if more frequent doses are preferred, two or four 50 mg doses may be given initially, followed by one 50 mg dose every 6 hours. Therapy should be continued for 1 or 2 days beyond the time when characteristic symptoms or fever have subsided.

For treatment of syphilis, AVA-MINOCYCLINE therapy should be administered over a period of 10 or 15 days. Close follow up, including laboratory tests, is recommended.

Concomitant therapy: Antacids containing aluminum, calcium or magnesium and/or iron preparations impair absorption and should not be given to patients taking minocycline.

PHARMACEUTICAL INFORMATION

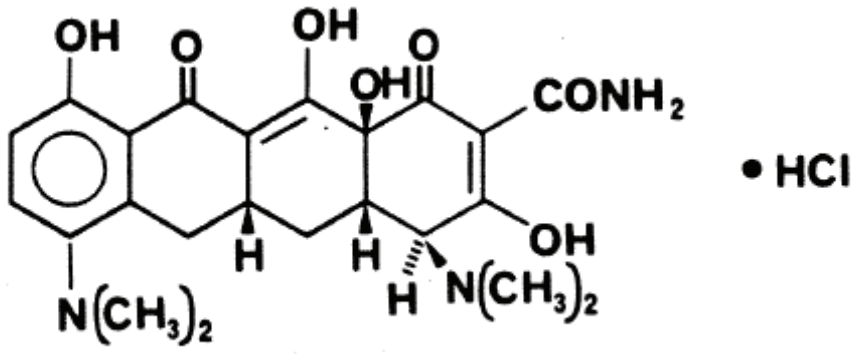
Drug Substance

Proper Name: minocycline hydrochloride

Chemical Names: 2-Naphthacenecarboxamide, 4, 7-bi s (dimethyl amino)-1, 4, 4a, 5, 5a, 6, 11, 12a-octahydro-3, 10, 12, 12a-tetrahydroxy-1,11-dioxo-, monohydrochloride, [4S-(4a, 4aa, 5aa, 12aa)] - .

4, 7-bis(dimethy1amino)-1, 4, 4a, 5, 5a, 6, 11, 12a-octahydro-3, 10, 12, 12a-tetrahydroxy-1, 11-dioxo-2-naphthacenecarboxamide monohydrochloride.

Structural Formula:



Molecular Formula: $C_{23}H_{27}N_30_7$.HCl
Molecular Weight: 493.94

Description: Minocycline hydrochloride is a yellow crystalline powder which is soluble in water and in solutions of alkali hydroxides and carbonates, slightly soluble in alcohol, and practically insoluble in chloroform and in ether.

Composition

In addition to the active ingredient minocycline, each capsule contains the non-medicinal ingredients lactose, croscarmellose sodium, stearic acid and magnesium stearate. The capsule shell contains the non-medicinal ingredients gelatin, sodium lauryl sulfate, FD&C yellow #6 and titanium dioxide. The 100 mg capsule, imprinted with edible white ink, also contains the non-medicinal ingredients FD&C blue #1 and FD&C red #3. The 50 mg capsule is imprinted with edible black ink containing the non-medicinal colourants FD&C blue #1, FD&C blue #2, FD&C red #40 and D&C yellow #10.

Stability and Storage Recommendations

Store at control led room temperature 15-30°C (59-86OF).

Protect from light. Protect blister packs from high humidity.

AVAILABILITY OF DOSAGE FORMS

Ava-minocycline Capsules 50 mg

Each orange capsule, imprinted 'APO 50', contains minocyline hydrochloride equivalent to 50 mg minocyline.

Available in bottles of 100.

Ava-minocycline Capsules 100 mg

Each orange and purple capsule, imprinted 'APO 100', contains minocycline hydrochloride equivalent to 100 mg minocycline.

Available in bottles of 100.

MICROBIOLOGY

Minocycline is a broad spectrum antibiotic and has been shown to be active in vitro against the following Gram-negative, Gram-positive and other micro-organisms:

Escherichia coli

Enterobacter aerogenes

Haemophilus influenzae

Klebsiella spp.
Streptococcus pyogenes (group A)
Streptococcus (group B)
Streptococcus pneumoniae
Staphylococcus epidermis
Staphylococcus aureus
Neisseria gonorrhoeae
Proteus spp.

In Vitro Activity

A survey of the in vitro activity of minocycline against clinical isolates was compiled from data presented in 130 articles published from 1967 to 1980. The MICs of minocycline against clinical isolates representing gram-positive, gram-negative, actinomycetes, acid-fast and anaerobic bacteria and mycoplasma, were recorded and entered into a computer data-base file. The percent of clinical isolates inhibited at various antibiotic concentrations was determined directly from the total number of isolates tested by a computer-assisted statistical analysis system program. The results are as follows:

BACTERIA	No. of Strains Tested	Cumulative % Strains Inhibited at the Indicated Concentrations of Minocycline (mg/L).			
		≤1	≤4	≤8	≤16
GRAM-POSITIVE					
Staphylococcus aureus	3301	77	91	96	98
Staphylococcus aureus - methicillin resistant	13	38	100		
Staphylococcus aureus - penicillin resistant	100	100			
Staphylococcus aureus - tetracycline resistant	736	50	75	84	93
Staphylococcus epidermidis	577	89	94	95	98

BACTERIA	No. of Strains Tested	Cumulative % Strains Inhibited at the Indicated Concentrations of Minocycline (mg/L).			
		≤1	≤4	≤8	≤16
Staphylococcus epidermidis - methicillin resistant	19	21	89	95	95
Staphylococcus species	775	82	89	96	99
Staphylococcus species - tetracycline resistant	46	48	100		
Streptococcus beta hemolytic	654	73	83	95	99
Streptococcus - Enterococcus group	844	18	23	28	46
Streptococcus pneumoniae	508	78	88	96	99
Streptococcus pneumoniae - tetracycline resistant	70	27	57	96	100

BACTERIA	No. of Strains Tested	Cumulative % Strains Inhibited at the Indicated Concentrations of Minocycline (mg/L).			
		≤1	≤4	≤8	≤16
GRAM-NEGATIVE					
Acinetobacter calcoaceticus	456	95	99	100	
Acinetobacter species	56	96	100		
Bordetella pertussis	23	100			
Brucella species	127	75	100		
Citrobacter species	37	8	81	81	84
Enterobacter aerogenes	130	0	13	35	61
Enterobacter cloacae	131	0	9	18	44
Enterobacter species	310	7	78	91	95
Escherichia coli	1538	33	56	69	78
Haemophilus influenzae	385	62	90	98	100
Haemophilus species	182	89	98	99	100

BACTERIA	No. of Strains Tested	Cumulative % Strains Inhibited at the Indicated Concentrations of Minocycline (mg/L).			
		≤1	≤4	≤8	≤16
Klebsiella - Enterobacter group	309	30	48	59	68
Klebsiella pneumoniae	299	2	35	53	69
Klebsiella species	247	7	49	62	74
Legionella pneumophila	21	62	100		
Neisseria gonorrhoeae	1082	97	100		
Neisseria gonorrhoeae - beta lactamase positive	50	90	100		
Neisseria meningitides	613	94	100		
Proteus – indole positive species	102	1	30	47	61
Proteus mirabilis	382	4	12	32	46
Providencia species	94	1	7	16	28
Pseudomonas aeruginosa	643	7	18	36	58
Pseudomonas cepacia	90	8	19	83	97
Pseudomonas maltophilia	81	85	99	99	99
Pseudomonas pseudomallei	157	10	77	89	92
Pseudomonas species	68	68	90	91	93
Salmonella species	128	2	59	76	80
Salmonella species - tetracycline resistant	123	0	73	92	100
Serratia species	341	0	23	37	55
Shigella species	90	28	66	80	86
Vibrio cholerae type Eltor	203	61	100		
Vibrio species	367	53	100		
Versinia species	212	94	100		

BACTERIA	No. of Strains Tested	Cumulative % Strains Inhibited at the Indicated Concentrations of Minocycline (mg/L).			
		≤1	≤4	≤8	≤16
ACID-FAST BACTERIA					
Mycobacterium tuberculosis	5	0	0	80	100
Mycobacterium species	90	4	26	71	74
ACTINOMYCETES					
Actinomyces Israeli	31	100			
Actinomyces species	110	89	95	100	
Nocardia asteroids	84	1	89	100	
Nocardia species	74	30	91	99	100
MYCOPLASMA					
Mycoplasma pneumoniae	14	100			
Mycoplasma species	223	85	91	92	93
CHLAMYDIA					
Chlamydia trachomatis	3	100			

BACTERIA	No. of Strains Tested	Cumulative % Strains Inhibited at the Indicated Concentrations of Minocycline (mg/L).			
		≤1	≤4	≤8	≤16
ANAEROBIC					
Bacteroides fragilis	673	44	80	97	99
Bacteroides species	431	58	77	90	92
Campylobacter fetus	97	90	91	91	91
Clostridium species	297	69	81	91	98
Eubacterium species	144	53	87	99	100
Fusobacterium species	107	66	94	100	
Peptococcus species	375	46	81	97	99
Peptostreptococcus species	242	59	85	99	99
Propionibacterium acnes	102	89	95	100	
Propionibacterium species	70	94	97	99	100
Veillonella species	13	69	92	100	

SUSCEPTIBILITY TESTING

Tube-Dilution Testing:

Microorganisms may be considered susceptible (likely to respond to minocycline therapy), moderately susceptible (harbouring partial resistance) or resistant (not likely to respond to minocycline therapy) depending on the minimum inhibitory concentration (M.I.C.) as follows:

Minocycline M. I .C. Interpretive Standards (mg/L)

Susceptible	Moderately Susceptible	Resistant
≤4	8	≥16

Acceptable Quality Control Ranges of M.I.C. for Reference Strains:

Reference Strain	ATCC NUMBER	mg/mL
Staphylococcus aureus	29213	0.12 - 0.5
Streptococcus faecalis	29212	2.0 - 8.0
Escherichia coli	25922	0.5 - 2.0

Plate Testing:

If the Kirby-Bauer method of susceptibility testing (using a 30 mcg tetracycline disc) gives a zone of 19 mm or greater, the bacterial strain is considered to be susceptible to any tetracycline. A zone of 14 mm or less is considered resistant.

Zone diameter Interpretive Standards (30 mcg disc)

Susceptible	Moderately Susceptible	Resistant
≥19 mm	15 – 18 mm	≤14 mm

For Staphylococcal species, minocycline powder may be used for additional susceptibility testing.

Acceptable Quality Control Limits (Zone Diameter) for Disc Susceptibility testing of reference strains:

Reference Strain	ATCC NUMBER	Zone Diameter (mm)
Escherichia coli	25922	19 - 25
Staphylococcus aureus	25923	25 - 30

PHARMACOLOGY

Animal Pharmacology:

Blood levels produced following oral dosing of minocycline to various animal species were: 21 mg/L at steady state in monkeys administered 30 mg/kg, and 6.5 mg/L at 3 hours post-dose in rats given a single 25 mg/kg dose. Minocycline was extensively distributed to all tissues examined in ^{14}C-label led drug studies in dogs.

Human Pharmacology:

Following a 200 mg oral loading dose of minocycline, serum levels are detectable within the first hour, reach 95% levels at 1 hour, and peak concentrations of 2-4 µg/mL at 2 hours. At the end of 24 hours the serum levels are approximately 1 µg/mL. Maintenance of levels in the 2.3 to 3.5 µg/mL range occurs when the loading dose is followed by a maintenance dose of 100 mg every 12 hours.

When given 200 mg once daily for three days the serum levels had fallen to approximately 1 µg/mL at 24 hours. After a single oral dose of 150 mg, minocycline has a serum half-life of 16 hours.

TOXICOLOGY

Minocycline has been tested in acute experiments in mice and rats, sub-chronic and chronic experiments in rats and dogs following oral and parenteral routes of administration.

The LD_{50} of intravenous and intraperitoneal injections of minocycline in mice was 95 mg/kg and 280 mg/kg, respectively. The oral LD_{50} in mice was 3100 mg/kg.

Minocycline has been given orally each day t o dogs for six months at doses of 0, 4, 20 and 60 mg/kg/day (100 mg/kg/day for the first month) equally divided each day. At 20 mg/kg/day, there were no apparent drug-related findings except yellow discolouration of the skeleton and teeth in some animals, occasional emesis and black discoloration of the thyroid gland. At a dose of 4 mg/kg/day, there were no drug-related findings during the six month period, with the exception of discolouration of the thyroid gland and possibly some yellowing of the bones. Peak serum drug concentrations ranging from 8.5 t o 100 mg/L were obtained with 60 and 100 mg/kg/day doses, 2.1 t o 9.7 mg/L with the 20 mg/kg/day dose and 0.4 t o 1.5 mg/L with the 4 mg/kg/day dose.

Minocycline was also given intravenously to dogs at doses of 5, 10, 20 and 40 mg/kg/day, a very similar dose range to that of the oral study, but administered for 1 month. Untoward findings such as body weight loss, reduced food consumption, erythema of the skin and of visible mucous membranes of varying duration, intensity and incidence, were associated primarily with the high dose (40 mg/kg/day). These findings were similar, except for erythema, to those obtained after the same dose of tetracycline. These drug-related findings with minocycline were associated with serum concentrations of 95 mg/L, three times those found with tetracycline (31 mg/L). Dogs that received 5, 10 and 20 mg/kg/day intravenously gave serum concentrations of 4, 12 and 38 mg/L,

respectively, and were found essentially to be without toxicity. These serum values are in considerable excess of those necessary for therapeutic effectiveness in man. In these experiments, minocycline appeared to be tolerated as well intravenously as it was orally.

Similar results were found following chronic oral administration of minocycline to rats for one year. These animals were given a drug diet containing 0.008, 0.04, 0.2 and 1.0% minocycline, which corresponded to ranges of 4.4 to 8.5, 21.3 to 44.0, 108 to 122 and 593 to 812 mg/kg/day drug intake; these doses gave early morning plasma drug concentrations of 0.07 to 0.16, 0.36 to 0.51, 2.9 to 6.5 and 17 to 50 mg/L, respectively. With the exception of the discolouration of the teeth (dose 0.04% drug diet or greater), femur and thyroid gland, there were no significant drug-related signs of toxicity at doses less than 1% drug diet.

As with other tetracyclines, minocycline has been found to produce discolouration of the thyroid gland in the rat, dog, monkey and human but not in the mouse. There was no evidence, however, from these investigations that thyroid function or bone growth was affected. A 23-month carcinogenicity study in the rat has shown that minocycline was not carcinogenic and that the black pigment in the thyroid gland did not cause neoplastic changes.

Biopsy specimens of thyroid tissue following the administration of minocycline and tetracycl ine to man revealed an intraepithelial lipofuscin deposition of both drugs, considered to be within normal variation. Thyroid function studies in man displayed a decrease within the normal range of thyroxine, indicating a tendency toward relative hypothyroidism.

Other than the tooth and bone discolouration that also occurs with other tetracyclines and the thyroid pigmentation seen in rats, dogs and monkeys, toxic effects of minocycline were observed only where serum concentrations were in excess of the therapeutic concentrations. It is concluded from the chronic safety evaluation studies that minocycline has a good margin of safety between therapeutic blood concentrations and concentrations producing toxic effects.

Reproduction studies performed in rats, rabbits and dogs have shown, as with other tetracyclines in animal studies, that minocycline crosses the placenta, is found in fetal tissues and can produce toxic effects on the developing embryo, fetus or neonate when present in sufficient amounts.

The effects observed on the conceptus in rats and rabbits ranged from a low incidence of slight retardation of ossification and slight angulation of ribs at oral doses of 70 mg/kg/day in rats and 25 mg/kg/day in rabbits during pregnancy, to more extensive retardation of ossification and generalized morphologic changes and death at doses of 150 mg/kg/day and higher in the rat fetus. In other experiments, no deleterious effects were reported in rats or rabbits with oral doses as high as 100 and 75 mg/kg/day respectively. No adverse effects due to minocycline were seen in the newborn of 2 dogs given 20 mg/kg in 2 equally divided daily doses from days 35 to 62 of pregnancy.

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