PRODUCT MONOGRAPH

pms-MINOCYCLINE

(MINOCYCLINE HYDROCHLORIDE CAPSULES USP)

50 mg & 100 mg

ANTIBIOTIC

Pharmascience Inc.
6111 Royalmount Avenue, suite 100
Montréal, Canada
H4P 2T4

Date of Preparation:
December 8, 1998
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July 29, 2004

Control Number: 090784

PRODUCT MONOGRAPH

pms-MINOCYCLINE
(Minocycline Hydrochloride Capsules USP)
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THERAPEUTIC CLASSIFICATION

Antibiotic

ACTION AND CLINICAL PHARMACOLOGY

Minocycline is a tetracycline with antibacterial activity against some gram-negative and gram-positive organisms. The action of minocycline is primarily bacteriostatic and it is thought to exert its antimicrobial effect by the inhibition of protein synthesis.

A bioavailability study comparing two different formulations of minocycline was performed. Pharmacokinetic and bioavailabilty data of pms-MINOCYCLINE were measured from volunteers in the fasting state after a single 200 mg (2 x 100 mg capsules) dose of pms-MINOCYCLINE was administered. The results can be summarized as follows:

Summary Table of the Comparative Bioavailability Data of
pms-MINOCYCLINE 100 mg Capsules (Pharmascience Inc., Canada, Lot# C-0010)
versus
Minocin 100 mg Capsules (Lederle-Cyanamid Canada Inc., Lot# 4K0494)

Measured Data of Minocycline

Parameter	Geometric Mean Arithmetic Mean (C.V.%) Test	Reference	Ratio of Means (%) (90% Confidence Limits)
AUC_T (µg·h/mL)	38.82 39.21 (14.4)	38.64 38.98 (13.5)	100.5 (97.8-103.2)
AUC∞ (µg·h/mL)	41.53 42.00 (15.4)	41.36 41.80 (15.0)	100.4 (97.4-103.6)
C_{max} (µg/mL)	1.948 1.968 (15.0)	1.882 1.897 (13.4)	103.5 (99.5-107.6)
T_{max} (h)	2.35 (0.78)	2.21 (0.62)	---
$T½_{el}$ (h)	18.58 (2.71)	18.58 (2.76)	---

For the T_{max} and $T½_{el}$ parameters these are the arithmetic means with standard deviation in parenthesis.

INDICATIONS AND CLINICAL USES

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

Gall bladder infections caused by Escherichia coli.

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

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 children under the age of thirteen years) has been shown to cause permanent tooth discoloration (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 to retardation of skeletal development).

Evidence of embryotoxicity 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, hypophosphatemia and acidosis.

Renal failure, including interstitial nephritis has been reported rarely.

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.

Reduced efficacy and increased incidence of breakthrough bleeding has been suggested with concomitant use of tetracycline and oral contraceptive preparations.

PRECAUTIONS

The administration of minocycline 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. (See Adverse Reactions).

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 indicate that photosensitivity is rarely reported with minocycline.

Patients treated with minocycline may suffer from headaches, light-headedness, dizziness or vertigo.

Decreased hearing has been rarely reported in patients on minocycline. 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 micro-organisms. 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 micro-organisms 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, pancreatitis, pruritis ani, constipation, dysphagia, inflammatory lesions (with monilial overgrowth) in the anogenital region, increases in liver enzymes, and rarely hepatitis and acute liver failure have been reported. Rare instances of esophagitis and esophageal ulcer-actions have been reported in patients taking the tetracycline-class antibiotics in capsule and tablet form. Most of these patients took the medication immediately before going to bed.

(c) Teeth and Bone: dental staining (yellow-grey-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 13 years. Enamel hypoplasia has also been reported. Discoloration 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. Renal failure, including interstitial nephritis has been reported rarely.

(e) Skin: maculopapular and erythematous rashes. Rarely reported - exfoliative dermatitis, onycholysis, discoloration of the nails, pigmentation of the skin and mucous membrane, erythema multiforme, Stevens-Johnson syndrome. Lesions occurring on the glans penis have caused balanitis.

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

(g) Pseudotumor cerebri (benign intracranial hypertension) in adults has been associated with the use of tetracyclines. The usual clinical manifestations are headache and blurred vision. Bulging fontanels have been associated with the use of tetracyclines in infants. While both of these conditions and related symptoms usually resolve soon after discontinuation of the tetracycline, the possibility for permanent sequelae exists.

(h) 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 discoloration 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, aluminum 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 pms-MINOCYCLINE 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 pms-MINOCYCLINE is 100 mg or 200 mg initially, followed by 100 mg every 12 hours. Alternatively, if more frequent doses are preferred, 2 or 4 doses of 50 mg 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, 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

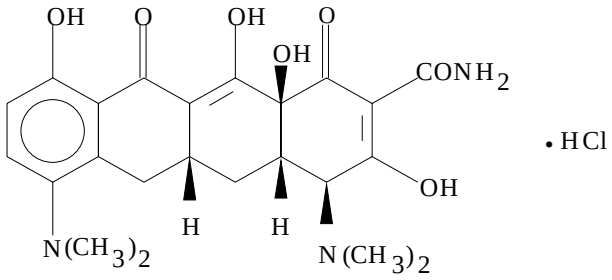
Drug Substance:

Proper Name: Minocycline Hydrochloride

Trade Name: pms-MINOCYCLINE

Chemical Name: 4,7-Bis(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3, 10,12,12a-tetrahydroxy-1,11-dioxo-2-naphtacenecarboxamide monohydrochloride.

Structural Formula:



Molecular Formula:

$C_{23}H_{27}N_30 \cdot HCl$

Molecular Weight: 493.94

Description: Minocycline hydrochloride is a yellow crystalline powder which is slightly hydroscopic and slightly sensitive to light and oxidation.

Composition:

Non-Medicinal Ingredients:

Each 50 and 100 mg capsule of pms-MINOCYCLINE contains polyethylene glycol 4 000 BP, polyethylene glycol 10 000 BP. In addition the capsule shells contain gelatin, titanium dioxide, D&C Yellow #10, FD&C Yellow #6 [100 mg only], FD&C Red #40, FD & C blue #1[100mg only] and D & C red #28.

Stability And Storage Recommendations:

Store at controlled room temperature 15°-30°C.

AVAILABILITY OF DOSAGE FORMS

pms-MINOCYCLINE 50 mg Capsules are available in bottles of 100, 250 and 500. Each capsule with orange opaque cap and body is imprinted "P" and "50" on both cap and body, in black ink.

pms-MINOCYCLINE 100 mg Capsules are available in bottles of 50, 100, 250 and 500. Each capsule with purple opaque cap and orange opaque body is imprinted "P" and "100 " on both cap and body, in white ink.

Potency is calculated in terms of minocycline base.

MICROBIOLOGY

This 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.

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
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	9599
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 aeroqenes	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
Klebsiella- Enterobacter group	309	30	48	59	68
Klebsiella pneumoniae	299		2	35	5369
Klebsiella species	247	7	49	62	74
Legionella pneumophila	21	62	100		
Neisseria gonorrhoea	1082	97	100		
Neisseria gonorrhoea - beta lactamase positive	50	90	100		
Neisseria meningitidis	613		94	100	

Proteus indole positive species		102		1	30	4761
Proteus mirabilis	382		4	12	32	46

BACTERIA	No. of Strains Tested	Cumulative % Strains Inhibited at the Indicated Concentrations of Minocycline (mg/L). ≤1	≤4	≤8	≤16
GRAM-NEGATIVE					
Providencia species	94	1	7	16	28
Pseudomonas aeruginosa	643	7	18	36	58
Pseudomonas cepacia	90		8	19	8397
Pseudomonas maltophilia	81	89	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	
Yersinia species	212	94	100		

Concentrations BACTERIA	No. of Strains Tested	Cumulative % Strains Inhibited at the Indicated 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 asteroides	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
Peptostretococcus 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: Micro-organisms may be considered susceptible (likely to respond to minocycline therapy), moderately susceptible (harboring 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.l.C. for Reference Strains:

Reference Strain	ATCC NUMBER	mg/L
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-labelled drug studies in dogs.

Human Pharmacology: Serum concentrations in normal adults given a single 200 mg capsule averaged 2.24 (0.74 - 4.45) mg/L at one hour and 1.25 (0.34 - 2.36) mg/L at 12 hours. After a single oral dose of 150 mg, minocycline has a serum half-life of about 16 hours. In a group of 5 healthy male volunteers, serum levels of 1.4 - 1.8 mg/L were maintained at 12 and 24 hours with doses of 100 mg every 12 hours for three days. When given 200 mg once daily for three days, the serum levels had fallen to approximately 1 mg/L at 24 hours.

When Minocycline Hydrochloride Tablets are administered with a meal including milk, the extent of absorption (AUC) is reduced by approximately 33% while the peak serum concentrations are reduced by approximately 32% and delayed one hour. In previous studies with other dosage forms,

the minocycline half-life ranged from 11 to 16 hours in 7 patients with hepatic dysfunction, and from 18 to 69 hours in 5 patients with renal dysfunction. The urinary and fecal recovery of minocycline when administered to 12 normal volunteers is one-half to one-third that of other tetracyclines.

TOXICOLOGY

Minocycline has been tested in acute experiments in mice and rats, and in 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 to 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 discoloration 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 discoloration of the thyroid gland and possibly some yellowing of the bones. Peak serum drug concentrations ranging from 8.5 to 100 mg/L were obtained with 60 and 100 mg/kg/day doses, 2.1 to 9.7 mg/L with the 20 mg/kg/day dose and 0.4 to 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 discoloration 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 discoloration 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 showed 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 tetracycline 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 discoloration 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. On 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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