

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-038

PHARMACOLOGY REVIEW(S)

N21038

on #21-038

HFD-170

K1.4



DRUG NAME: Precedex (dexmedetomidine hcl injection)

APPLICANT: ABBOTT LABORATORIES

REC.
12/28/99

CHEMICAL & THERAPEUTIC CLASS:1S

Review Cycles

Review Cycle: 1 Submission Date:12-18-98 Receipt Date:12-18-98 Goal Date:12-18-99 Action:AP	Review Cycle: 2 Submission Date: Receipt Date: Goal Date: Action:
Review Cycle: 3 Submission Date: Receipt Date: Goal Date: Action:	Review Cycle: 4 Submission Date: Receipt Date: Goal Date: Action:

CORE REVIEW TEAM MEMBERS

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CHEMISTRY:Michael Theodorakis, Ph.D.
PHARM/TOX:Harry Geyer, Ph.D.
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Volume 4 of 4

Administrative volume #(s): 1

Clinical volume #(s): 2

CMC volume #(s): 3

Pharmacology/Toxicology volume #(s): 4

ODE II ACTION PACKAGE TABLE OF CONTENTS

Application #21-038

Drug Name: Precedex (dexmedetomidine Hydrochloride injection), 2 mL ampule/2 mL vial, 100 mcg/mL

Applicant: Abbott Laboratories

Chem./Ther. Type: 1S

CSO/PM: Susmita Samanta

Phone: 301-827-7410

HFD-170

Original Application Date: December 18, 1998 Original Receipt Date: December 18, 1998

CURRENT USER FEE GOAL DATE: December 18, 1999 Date Table of Contents Completed: 9/13/99

Section A:

Administrative Information

X (completed),
N/A (not applicable),
or Comment

Tab A-1	Action Letter(s)	Current Action: AP _____	X
Tab A-2	Phase 4 Commitments:		
	a.	Copy of applicants communication committing to Phase 4	NA
	b.	Agency Correspondence requesting Phase 4 Commitments	NA
Tab A-3	FDA revised Labels & Labeling and Reviews: (Separate each version/cycle with a colored sheet)		
	a.	Package Insert	X
	b.	Immediate Container and Carton Labels	NA
Tab A-4	Original Proposed Labeling		X
Tab A-5	Foreign Labeling:		
	a.	Foreign Marketing History	NA
	b.	Foreign Labeling and Review(s)	NA
Tab A-6	Labeling and Nomenclature Committee's Tradename Review		X
Tab A-7	Summary Memoranda (e.g., Division Director, Group Leader, Office)		X
Tab A-8	Copy of Patent Statement		X
	Exclusivity Checklist (and any requests for exclusivity)		X
	Debarment Statements		X
Tab A-9	Correspondences, Faxes, & Telecons		X
Tab A-10	Minutes of Meetings:		
	a.	End-of-Phase II meeting	NA
	b.	Pre-NDA meeting(s)	NA
	c.	Filing meeting	X
	d.	Other meetings	X
Tab A-11	Advisory Committee Meeting:		
	a.	Questions Considered by the committee	NA
	b.	List of Attendees	NA
	c.	24 hour alert memorandum	NA
Tab A-12	Project Management Administrative Information (optional)		

ODE II ACTION PACKAGE TABLE OF CONTENTS (continued)

Application #21-038 Drug Name: Dexmedetomidine HCL

Section B:

Clinical Information

X (completed),
N/A (not applicable),
or Comment

Tab B-1	Clinical Reviews and Memoranda
Tab B-2	Safety Update Reviews
Tab B-3	Pediatric Page
Tab B-4	Statistical (Clinical) Review and Memoranda
Tab B-5	Biopharmaceutics Review and Memoranda
Tab B-6	Abuse Liability Review
Tab B-7	DSI Audits
Tab B-8	Summary of Efficacy (from the summary volume of the application)
Tab B-9	Summary of Safety (from the summary volume of the application)

X
X
X
X
X
X
X
NA
NA

Section C:

Chemistry, Manufacturing, and Controls (CMC) Information

X (completed),
N/A (not applicable),
or Comment

Tab C-1	CMC Reviews and Memoranda
Tab C-2	DMF Reviews
Tab C-3	EA Reviews/FONSI
Tab C-4	Micro Review (validation of sterilization)
Tab C-5	Statistical Review of drug stability
Tab C-6	Inspection of facilities => Decision: _____ Date: _____
Tab C-7	Methods Validation Information

X
X
X
X
NA
X
PENDING

Section D:

Pharmacology/Toxicology Information

X (completed),
N/A (not applicable),
or Comment

Tab D-1	Pharmacology/Toxicology Reviews and Memoranda
Tab D-2	Carcinogenicity Review (statistical)
Tab D-3	CAC/Executive Committee Report

X
NA
NA

ADDITIONAL NOTES:



FDA CENTER FOR DRUG EVALUATION AND RESEARCH

DIVISION OF ANESTHETIC, CRITICAL CARE, AND ADDICTION DRUG PRODUCTS

HFD-170, Room 9B-45, 5600 Fishers Lane, Rockville MD 20857

Tel:(301)443-3741

MEMORANDUM

DATE: November 30, 1999

TO: Dr. Cynthia McCormick

FROM: Dr. Lucy Jean 151

RE: Team Leader's Summary of NDA 21-038

Introduction: Dexmedetomidine HCl (DEX) is a potent (7x clonidine), and selective α_2 -agonist. The drug is to be marketed as a parenteral solution (Trade name) for intravenous infusion. The indication is for supplemental sedation and/or analgesia in ICU for up to 24 hours. The recommended doses are a loading dose of $1 \mu\text{g}/\text{kg}$ over 10 minutes, followed by a maintenance infusion of 0.2 to $0.7 \mu\text{g}/\text{kg}/\text{hr}$ to the desired level of sedation and/or analgesia.

Efficacy: In the CNS via α_2 -agonist activity, DEX produces sedation, analgesia and reduced anxiety. The sedative/hypnotic ($10\text{-}30 \mu\text{g}/\text{kg}$ iv), analgesic ($3\text{-}6 \mu\text{g}/\text{kg}$ iv) and anxiolytic ($0.3\text{-}2 \mu\text{g}/\text{kg}$ iv) effects were shown in mice and rats; and in dogs the sedative/hypnotic effects as well. No anticonvulsant activity was shown. In rats ($3 \mu\text{g}/\text{kg}$ i.v.) DEX reduced ischemic brain damage.

Safety pharmacology: The α_2 -agonist inhibits the release of norepinephrine at neurons. Thus DEX, via its α_2 -agonist activity in the CNS; inhibits sympathetic activity resulting in decreases of blood pressure and heart rate. The CV effects of dec BP & HR were observed in rats, dogs and monkeys. In dogs ($1 \mu\text{g}/\text{kg}$ iv), decreases of the heart rate, myocardial contractility, CO, and oxygen demand by the heart (increased AV O_2 saturation) were observed. Similar to some of the imidazole-derivates of intravenous anesthetics, suppression of the HPA was observed only following prolonged infusion. In dogs prolonged sc infusion ($10 \mu\text{g}/\text{kg}/\text{hr}$ for 7 days) of DEX decreased the ACTH-stimulated cortisol level by 40%, but no effect was observed following single sc dose of

80 µg/kg. Glucosuria and transient hyperglycemia in rats, gerbils or rabbits are considered drug-class effects, since clonidine also shows similar changes. The effects may be species specific, as the available clinical data did not show these adverse effects.

Special Toxicology Studies: No hemolytic potential was shown in an in vitro study. Levomedetomidine, the principal impurity in clinical drug product, was shown to have low order of toxicity in both rats and dogs following 4-wk of daily iv administration; the NOAELs were at 625 and 400 µg/kg, respectively. Presence of this impurity at 1% in the drug product should not pose safety concern.

ADME/Pharmacokinetics: Pharmacokinetics and excretion are similar in humans and animal species; but metabolism is significantly species specific. Absorption was rapid in rats and dogs following im or sc administration with T_{max} less than an hour. Following iv, T_{1/2} was approximately 2.5 hrs (humans), 1.5 hrs (rat & dog). The extent of plasma protein binding was high in human, rat and dog (94%, 88% and 93%, respectively). No significant displacement of other protein-bound drugs was observed. In rats, tissue distribution was rapid and the highest levels were in the adrenal, liver and kidneys. By 72 hrs the tissue levels were low. DEX was extensively metabolized in both humans, rats and dogs. All species shared a common pathway of N-methylation at 3-methyl position, followed by hydroxylation (forming 3-hydroxy N-methyl), then oxidation (forming carboxy-N-methyl) or glucuronidation (N-methyl o-glucuronide). But significant species specific metabolism was present. In humans, direct N-glucuronidation of the imidazole-N was the major metabolic pathway. The two major metabolites formed, (the N-glucuronides of imidazole nitrogen and N-methyl-O-glucuronide) were not detected in rats or dogs. In animal species besides glucuronides, sulfate, mercapturate and glutathione conjugates of the 3-methyl hydroxyl were also detected.

Toxicology: Acute and 4-wk repeated-dose toxicity studies were carried out in rats and dogs following various routes of administration. The acute toxicity of rapid intravenous bolus injections was low in animals, as 1000 µg/kg was not lethal to mice, rats or dogs. The clinical signs at high doses included sedation, piloerection, exophthalmos, salivation, tachypnea and clonic convulsion. Four-week repeated-dose toxicity studies in rats and dogs were carried out following daily iv and im bolus administration. Significant drug-related target organ toxicities or adverse effects were as follows: (1) Liver: apparent only in dogs with elevated liver enzymes (ALT, GGT), eosinophilic intracytoplasmic inclusions, hepatic apoptotic bodies at 50-250 µg/kg/d. In rats and dogs, dose-related increased liver absolute and relative weights; but no enzyme elevation or histopathological findings in rats; (2) Lungs (in rats only): dose-related increases in hemosiderin-laden macrophages, possible reflecting some pulmonary inflammation; (3) Adrenals (in rats only): hypertrophy of zona glomerulosa, reflecting increased mineralocorticoid secretion; (4) Eyes (in dogs and rats): corneal cloudiness or opacities (keratitis) caused by loss of blinking reflex and dryness (from α₂ - agonist related sedation/analgesia/decreased lacrimation); (5) Reduced organ weights: in high-dose rats only: testes, seminal vesicles, prostate, epididymis, uterus; and in rats and dogs

thymus: dose related weight decreases with no histopathology; (6) Injection site irritations (in dogs and rats): intravascular and perivascular fibrosis (iv), hemorrhages (all routes), and granulation (im, sc). The NOAELs in rats (20 $\mu\text{g}/\text{kg}/\text{day}$ im and sc and 10 $\mu\text{g}/\text{kg}/\text{day}$ iv) and in dogs (10 $\mu\text{g}/\text{kg}/\text{day}$ im and iv) are less than the MRHID on a mg/m^2 basis. The LOAELs in rats (100 $\mu\text{g}/\text{kg}$ im and sc and 40 $\mu\text{g}/\text{kg}$ iv) and in dogs (50 $\mu\text{g}/\text{kg}$ im and iv) are approximately 14X (rat/iv) and 56X (dog/iv) the MRHID on a mg/m^2 basis.

Reproductive Effects: DEX is not teratogenic in rats (200 mcg/kg/d sc rats = 2X MRHID on a mg/m^2 basis) and rabbits (96 mcg/kg/d iv = MRHID). Fetal toxicity, as evidenced by increased postimplantation losses and reduced the number of live pups per litter, was observed in rats (200 mcg/kg/d sc rats = 2X MRHID). The NOAEL was 20 mcg/kg/d (less than MRHID). Prenatal and postnatal effects included reduced pup body weights during and after nursing (8-32 mcg/kg/d) and delayed motor development (32 mcg/kg/d); the NOAEL was 2 mcg/kg/day (less than MRHID). Placental transfer occurred in rats.

Genotoxic Effects: DEX was not mutagenic in Ames mutation assay with *S. typhimurium* or *E. coli* and in mouse lymphoma assay. DEX was shown to be clastogenic in both the *in vitro* human lymphocytes chromosomal aberration assay in the presence of metabolic activation and *in vivo* mouse micronucleus assay.

CONCLUSIONS and RECOMMENDATIONS: Taking the data together and considering the different duration (4-wk vs 24-hr) and mode of administration (bolus vs infusion) in animal testings vs human use, it can be concluded that the pharmacological and toxicological profiles generated in the laboratory animals support the efficacy and reasonable safety that DEX can be labeled for human use. It should be noted that human metabolizes the compound differently from the animal species, the available clinical data also support the labeled usage of DEX. The pertinent nonclinical sections of the package insert have been amended.

Nonclinical issues:

(A) The pertinent nonclinical sections of the sponsor's proposed package insert have been amended by the reviewer.

(B) Phase IV studies:

(1) To mimic the human clinical infusion use, the sponsor has agreed to conduct two infusion studies in dogs. The first two-week study with a 2-week recovery phase is to evaluate the general toxicology and effect on HPA axis. The second study is to determine changes in drug metabolism following two weeks of infusion. The protocols

were reviewed.

(2) If, in the future, the product will be used for prolonged infusion in ICU, the potential toxicity of human major metabolites which are absent in rats and dogs should be addressed.

Because of species specific in metabolism, two human major metabolites (the N-glucuronides of imidazole nitrogen and N-methyl-O-glucuronide), absent in the rat and dog, were never studied in animals. If the drug product will be used in ICU for longer than 24 hrs of infusion, the potential toxicity of these human metabolites should be addressed in Phase IV animal studies following long-term infusion. The studies can be conducted following either a successful search for a human-relevant animal species in terms of metabolism, or alternatively the toxicity of the human metabolites can be studied in animal species following direct administration of these metabolites in an appropriate animal species.

**APPEARS THIS WAY
ON ORIGINAL**

**REVIEW AND EVALUATION
OF PHARMACOLOGY/TOXICOLOGY DATA**

NDA 21-038

INTRODUCTION	2
PHARMACOLOGY	15
PHARMACOKINETICS/TOXICOKINETICS/ADME	54
TOXICOLOGY	106
REPRODUCTIVE TOXICOLOGY	134
GENETIC TOXICOLOGY	149
SPECIAL TOXICOLOGY STUDIES	163
ANCILLARY STUDIES FROM THE LITERATURE	176
OVERALL SUMMARY AND EVALUATION	181
CONCLUSIONS	191
RECOMMENDATIONS	191

REVIEW AND EVALUATION OF PHARMACOLOGY/TOXICOLOGY DATA

Reviewer Name: Harry M. Geyer, III Ph.D.

Division Name: Division of Anesthetic, Critical Care & Addiction Drug Products
HFD# 170

Review Completion Date: September 20, 1999

NDA number: 21-038

Serial number/date/type of submission: 000/December 18, 1998/NDA original submission
NDA 21-038 BZ - July 6, 1999

Sponsor: Abbott Laboratories
Abbott Park, IL, 60064

Manufacturer for drug substance: Orion Corporation: Espoo, Finland

Drug:

Code Name: MPV-1440

Generic Name: dexmedetomidine HCl

Trade Name: _____

Chemical Name: (+)-4-[2,3-dimethylphenyl]ethyl]-1H-imidazole hydrochloride

CAS Registry Number: 113775-47-6 (base)

CAS Registry Number: 145108-58-3 (hydrochloride salt)

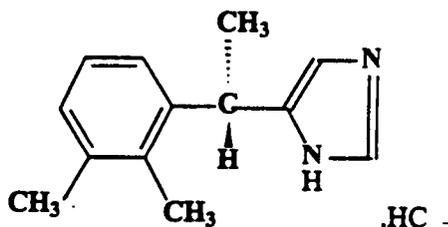
Molecular Formula/ Molecular Weight: $C_{13}H_{16}N_2 \cdot HCl$ / m.w. 236.7

Structure:

Relevant INDs/NDAs/DMFs:

dexmedetomidine

dexmedetomidine



**DEXMEDETOMIDINE
HYDROCHLORIDE
ABBOTT 85499.1**

Drug Class: α_2 adrenoreceptor agonist

Indication: sedative with analgesic properties for use in intensive care

NDA 21-038

Clinical formulation: clear isotonic solution pH 4.5 to 7.0, each milliliter contains 118 mcg of dexmedetomidine hydrochloride (100 mcg base) and 9 mg sodium chloride in water. The recommended dilution, for both loading dose and infusion, is 2 ml of dexmedetomidine solution into 48 ml of 0.9% saline. The infusion concentration is 4 mcg/ml.

Route of administration: intravenous infusion. Suggested loading dose = 1.0 ug/kg over 10 minutes and followed by 0.2 to 0.7 ug/kg/hr for as long as 24 hours.

Maximum recommended human intravenous dose (MRHD): _____
mg/m²/day

Disclaimer -- The sponsor's material was occasionally copied unchanged to avoid transcription errors.

Introduction

Dexmedetomidine, a congener of clonidine, is a potent, selective alpha₂-agonist, v _____
1. It is the dextro isomer of the racemate medetomidine and is about 7x the potency of clonidine at the alpha₂ receptor.

Dexmedetomidine has low or no affinity for dopaminergic, muscarinic or nicotinic cholinergic receptors, serotonin, GABA, histaminic, opioid mu or delta, benzodiazepines or sodium, potassium or calcium ion channels. There is also no affinity for the noradrenergic, dopaminergic or serotonergic reuptake receptors on the brain. The activity appears to be confined to the alpha₂ receptors. The alpha₂ receptors are located in the central nervous system (CNS), in autonomic ganglia, peripheral neurons and end-organs with sympathetic innervation. The alpha₂ activation of sympathetic neurons inhibits the release of norepinephrine and the alpha₂ in the CNS leads to inhibition of sympathetic activity, decreasing blood pressure and heart rate. The CNS mediated effects of sedation, ataxia and reduced anxiety have also been attributed to alpha₂ activation. Sedation in the ICU is the primary clinical use of this product.

Studies within this submission reviewed:

Review No.	NDA Study No.	Study	Review Page	NDA Vol / page
[1]	103.	Receptogram TM of six compounds	15	27/ 115
[2]	104.	Dexmedetomidine: affinity and activity on alpha ₂ -adrenoceptor subtypes.	17	27/ 272

NDA 21-038

[3]	162. The effects of dexmedetomidine N-glucuronides on alpha-2 adrenoceptors in vitro and in vivo. Study No. CN597122100010	18	30/ 001
[4]	127. Dexmedetomidine does not inhibit the activity of rat brain monoamine oxidase in vitro.	19	28/ 197
[5]	84. The metabolic effects of dexmedetomidine.	20	26/ 220
[6]	122. <u>A general pharmacology study of dexmedetomidine</u>	22	28/ 082
[7]	159. CNS general pharmacology profile in the mouse and the rat. Scientific Report Number R&D 96/500	23	29/ 155
[8]	78. The anticonvulsant and anticholinergic effects of dexmedetomidine.	25	26/ 166
[9]	80. Effect of dexmedetomidine against amygdala-kindled seizures	26	26/ 180
[10]	96. Neuroprotection by dexmedetomidine in rat focal ischemia - a comparative study with AMPA and NMDA receptor antagonists.	27	27/ 063
[11]	99. Neuroprotection by dexmedetomidine in gerbils	31	27/ 090
[12]	18. Effects of dexmedetomidine on motor-coordination and skeletal muscle tone in mice.	32	24/ 159
[13]	151. Treatment of ethanol withdrawal symptoms with subcutaneously administered dexmedetomidine, a selective alpha-2-adrenoceptor agonist.	33	29/ 065
[14]	152. Treatment of ethanol withdrawal symptoms with dexmedetomidine, a selective alpha-2-adrenoceptor agonist	34	29/ 095

NDA 21-038

[15]	47. The effect of dexmedetomidine on myocardial blood flow, metabolism and mechanical performance during short coronary occlusion and reperfusion in the dog. In: The effect of dexmedetomidine on the circulation and the normoxic and ischemic heart.	35	25/ 099
[16]	49. Comparison of the systemic hemodynamic and coronary vascular effects of dexmedetomidine in three animal experimental models. In: The effect of dexmedetomidine on the circulation and the normoxic and ischemic heart.	36	25/ 125
[17]	61. Comparison of the hemodynamic and coronary vascular effects of dexmedetomidine and clonidine in the anesthetized dog. In: The effect of dexmedetomidine on the circulation and the normoxic and ischemic heart.	39	26/ 001
[18]	65. Changes in cardiac function induced by dexmedetomidine, as determined by pressure-volume analysis. In; The effect of dexmedetomidine on the circulation and the normoxic and ischemic heart.	40	26/ 054
[19]	70. Comparison of hemodynamic stabilizing effects of dexmedetomidine and esmolol.	43	26/ 080
[20]	59. Effect of medetomidine either as the racemate mixture or as the individual stereo isomers on the heart rate of anesthetized rats.	48	25/ 204
[21]	177. Effects of α 2-adrenoceptor agonist dexmedetomidine on human platelet aggregation in vitro.	49	30/ 160
[22]	#4. Effects of dexmedetomidine on uterine contractions in rat NDA 21-038 BZ 7/6/99 V1/p67	50	
[23]	#12. Effects of medetomidine and dexmedetomidine on adrenocortical function in dogs. NDA 21-038 BZ 7/6/99 V1/p239	50	
[24]	186. Plasma Concentrations of Dexmedetomidine Following Subcutaneous Dosing in Rat. R&D/97/617	54	30/ 258
[25]	265. Pharmacokinetics of [³ H]-dexmedetomidine IV and IM in the rat.	55	46/ 384

NDA 21-038

[26]	187. Plasma Concentrations of Dexmedetomidine Following a Single IV or IM Dose in Dog. R&D/97/615	57	30/ 301
[27]	Abbott-85499 Drug Metabolism Report No.49 Effects of Age on the Plasma Concentrations of Dexmedetomidine following Subcutaneous Dosing in Rat V98-829 ; Report R&D 98/653	58	
[28]	Abbott-85499 Drug Metabolism Report No.49 Effects of Age on the Plasma Concentrations of Dexmedetomidine following Intravenous Dosing in Dog V98-830 Report: R&D/99/002	59	
[29]	237 Abbott-85499 Drug Metabolism Report No.5 - Plasma concentrations of Abbott-85499(dexmedetomidine)	60	42/ 237
[30]	188. Plasma Concentrations of Dexmedetomidine Following Intravenous Dosing in Rabbit. R&D/97/616	62	31/ 001
[31]	238. Abbott-85499 Drug Metabolism Report No.6 - Metabolism and excretion of [3H-dexmedetomidine (Abbott-85499) in rats (Protocol V95-031). Report No. R&D196/233	63	42/ 270
[32]	247. Abbott-85499 Drug Metabolism Report No. 7 - Tissue distribution of radioactivity in rats following a single intravenous 0.02 mg/kg dose of [3H]dexmedetomidine.HCl (Abbott-85499.1). Report No: R&D/96/720	66	44/ 001
[33]	261. Abbott-85499 Drug Metabolism Report No. 11 - Metabolism and excretion of [3H]dexmedetomidine following intravenous or subcutaneous administration to chronically bile duct cannulated rats (Protocol V96-014): Report No. R&D196/443.	69	45/ 221
[34]	250. Abbott-85499 Drug Metabolism Report No.28 - Metabolism of [3H]dexmedetomidine, [3H]levomedetomidine and [3H]medetomidine by precision-cut rat liver slices. Report No. R&D/971504	70	44/ 245

NDA 21-038

[35]	240. Abbott-85499 Drug Metabolism Report No.19 - Metabolism and disposition of [³ H]Abbott-85499.1 (dexmedetomidine.HCl) following subcutaneous and intravenous administration to dogs (Protocol V96-020). Report No. R&D/97/29.	73	42/ 367
[36]	251. Abbott-85499 Drug Metabolism Report No.25 - Metabolism of [³ H]dexmedetomidine, [3 H] levomedetomidine and [³ H]medetomidine by precision-cut dog liver slices. Report No. R&D/97/454	75	45/ 001
[37]	241. Abbott-85499 Drug Metabolism Report No.26 - Phase 1 study of the metabolism and excretion of [³ H]dexmedetomidine.HCl (Abbott-85499. 1) in normal male subjects (Protocol Dex-96-018). Report No. R&D/97/457	77	43/ 001
[38]	262. Pharmacokinetics and metabolic profiling of ³ H-labeled dexmedetomidine in healthy in male volunteers. Biometrical report. Study BA-91-04 (PBR-9 10208-4)	80	46/ 001
[39]	252. Pharmacokinetics and metabolic profiling of ³ H-labeled dexmedetomidine in healthy male volunteers. Metabolite profile of ³ H-dexmedetomidine in human urine. Study BA-91-04 (PBR-910208-4), DNO JSS9S05 1.	81	45/ 039
[40]	253. Abbott-85499 Drug Metabolism Report No.23 - Metabolism of [³ H]dexmedetomidine, [³ H]levomedetomidine and [³ H]medetomidine by precision-cut human liver slices. Report No. R&D/97/389,	82	45/ 065
[41]	254. Abbott-85499 Drug Metabolism Report No.36 - Identification of cytochrome P450 isoforms involved in the oxidative metabolism of dexmedetomidine (Abbott-85499) and the effect of dexmedetomidine on cytochrome P450-mediated monooxygenase activities. Report No. R&D/97/757	86	45/ 109
[42]	258. Abbott-85499 Drug Metabolism Report No.13 - The in vitro interaction of dexmedetomidine with human liver microsomal cytochrome P450 2D6 (CYP2D6).	89	45/ 179

NDA 21-038

[43]	242. Abbott-85499 Drug Metabolism Report No.8 - In vitro protein binding of [³ H]Abbott-85499 (dexmedetomidine) in mouse, rat, dog, monkey, and human plasma (Protocol V96-004)Report No. R&D/96/320	91	43/ 136
[44]	243. Abbott-85499 Drug Metabolism Report No.20 - In vitro binding of [³ H]Abbott-85499 (dexmedetomidine) to human serum albumin and (α_1 -acid glycoprotein) (Protocol V96-0 11). Report No. R&D/97/338,	92	43/ 161
[45]	244. Abbott-85499 Drug Metabolism Report No.29 - Protein binding interactions between Abbott-85499- ³ H (dexmedetomidine) and selected other drugs in human plasma (Protocol V97-034). Report No. R&D1971525	94	43/ 182
[46]	245. Abbott-85499 Drug Metabolism Report No.22 - Metabolism Report No.30 - Effect of Abbott-85499 (dexmedetomidine) on the protein binding of selected other drugs in human plasma (Protocol V97-027). Report No. R&D/971526	95	43/ 201
[47]	246. Abbott-85499 Drug Metabolism Report No.22 - In vitro determination of human red cell binding of Abbott-85499-3H (dexmedetomidine)(Protocol V97-026). Report No. R&D/97/371	96	43/ 221
[48]	256. Abbott-85499 Drug Metabolism Report No.27 - Conversion of [³ H]dexmedetomidine to [³ H] levomedetomidine in male subjects following a 2 ug/kg infusion of [³ H]dexmedetomidine.HCl Report No. R&D/97/458	97	45/ 153
[49]	212. Subacute Toxicity Study of Dexmedetomidine (MPV-1440 x HCl) by Daily Intramuscular Administration to Rats for 28 Days.	106	33/ 001
[50]	213. Subacute Toxicity Study of Dexmedetomidine (MPV-1440 x HCl) by Daily Intravenous Administration to Rats for 28 Days. TOX 89-020	112	34/ 001

NDA 21-038

[51]	215. Dexmedetomidine Hydrochloride: Subacute Toxicity Study by Daily Intramuscular Administration to Male Dogs for Four Weeks. TOX 90-006	116	35/ 190
[52]	216. Dexmedetomidine Hydrochloride: Subacute Toxicity Study by Daily Intramuscular Administration to Female Dogs for Four Weeks. TOX 90-013	120	36/ 001
[53]	222. Fourteen Day Intrathecal Toxicity Study of Dexmedetomidine in the Rat., TOX 94-019	123	37/ 001
[54]	223. A Pilot Intrathecal Injection Study of Dexmedetomidine Hydrochloride (Abbott- 84599 Hydrochloride) in the Beagle Dog. TB95-2 16, 1995.	124	37/ 112
[55]	224. A 28-Day Intrathecal Injection Toxicity Study of Dexmedetomidine Chloride (Abbott -85499 Hydrochloride) in the Beagle Dog with a 14-Day Recovery Period. TB95-224, 1995.	126	37/ 187 38/ 305
[56]	228. Fertility study (Segment I study) of Dexmedetomidine in Rats by Subcutaneous Administration. TOX 89-001, 1991.	134	40/ 147
[57]	230. Pre- and Post-Natal Study (Segment III study) of Dexmedetomidine in Rats by Subcutaneous Administration. TOX 90-017, 1994.	138	41/ 001
[58]	231. Examination of the Influence of MPV-1440 Hcl on the Pregnant Rabbit and the Foetus by Intravenous Administration. 5193/89, 1991.	141	42/ 001
[59]	248. Abbott-85499 Drug Metabolism Report No.31 - Lacteal excretion and fetal tissue distribution of radioactivity following a single subcutaneous dose of [³ H]dexmedetomidine.HCl (Abbott-85499. 1) in the rat (Study No. Covance 6161-175). Report No. R&D/97/565	143	44/ 149
[60]	232. Dexmedetomidine Hydrochloride. Bacterial Mutation Assay	149	42/ 082

NDA 21-038

[61]	233. Bacterial Reverse Mutation Assay of Dexmedetomidine Hydrochloride in Escherichia Coli.	150	42/ 107
[62]	234. Dexmedetomidine Hydrochloride. Mammalian Cell Mutation Assay FSG 19/931143, 1994.	151	42/ 130
[63]	235. Dexmedetomidine Hydrochloride. Metaphase Chromosome Analysis of Human Lymphocytes Cultured in vitro. FSG 18/93 206	153	42/ 168
[64]	200. Dexmedetomidine: Preliminary Dose-Range Finding Study for Mouse Micronucleus Test. TOX 95-007/1	156	31/ 125
[65]	199. Hypothermia Induces Micronuclei in Mouse Bone Marrow Cells. Mutation Res 1997;393:91-98.	157	31/ 117
[66]	198. Erythroid Hypoplasia in Bone Marrow Induced by Hypothermia in Mice. TOX 95-007/2	158	31/ 075
[67]	201. Micronucleus Test of Dexmedetomidine Hydrochloride in Mouse Bone Marrow. PT971 12100025	160	31/ 149
[68]	217. Local intramuscular Irritation Study of MPV-1440 (dexmedetomidine) in Rat. TOX 90-004/1	163	36/ 247
[69]	218. Acute Arterial Irritation Evaluation of Dexmedetomidine Hydrochloride in Rabbits. TE 95-284	164	36/ 276
[70]	219. Hemolysis test on Eight Formulations of MPV- 1440	165	36/ 298
[71]	220. Evaluation of Dexmedetomidine, Administered as the Hydrochloride Salt, for Passive Cutaneous Anaphylaxis in Guinea Pigs. TF95-009, 1995.	166	36/ 343
[72]	221. Evaluation of Dexmedetomidine, Administered as the Hydrochloride Salt, for Delayed Contact Hypersensitivity in Guinea Pigs (Draize Method). TF95-0 II	167	36/ 381
[73]	225. Subacute Toxicity Study of Levomedetomidine Hydrochloride by Daily Intravenous Administration to Female Rats for Two Weeks. TOX 91-032	168	38/ 306

NDA 21-038

[74]	226. MPV- 1441 (Levomedetomidine Hydrochloride) Subacute Toxicity Study by Daily Subcutaneous Administration to Rats for Four Weeks. TOX 88-029	170	39/ 001
[75]	227. Subacute Toxicity Study of MPV-1441 (Levomedetomidine Hydrochloride) by Daily Intravenous Administration to Dogs for 28 Days. TOX 96-002	171	39/ 249
[76]	Porter, David E. and Ogidigben. Miller J.; Medetomidine-Induced Alterations of Intraocular Pressure and Contraction of the Nictitating Membrane. Invest Ophth and Vis Sci 32(1):2799-2805, 1991 (#88)	176	27/ 006
[77]	Virttiainen J, MacDonald E, Uritti A, Rouhiainen H and Virtanen, R; Dexmedetomidine-Induced Ocular Hypotension in Rabbits With Normal or Elevated Intraocular Pressures Invest. Ophthamol & Vis Sci 33(6):2019-23(1992) (#87)	177	27/ 001
[78]	Savola J-M, Virtanen R; Central α_2 -adrenoreceptors are highly stereoselective for dexmedetomidine, the dextro enantiomer of medetomidine Eur J Pharmacol 195: 193-199 (1991) (#4)	178	24/ 019
[79]	Sabbe MB, Penn mg JP, Ozaki GT, Yaksh TL. "Spinal and Systemic action of the α_2 Receptor Agonist Dexmedetomidine in Dogs - Antinociception and Carbon Dioxide Response" Anesthesiology 80:1057-72 (1994) (#6)	179	24/ 033

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7. Viitamaa T. The anxiolytic effects of medetomidine and dexmedetomidine in a rat conflict test. Orion Pharm. Report; 7 November 1983.	24	49
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NDA 21-038

37. Ruskoaho H. Effect of dexmedetomidine on coronary vascular tone, heart rate and contractile force in the isolated perfused rat heart. Orion Pharm. Report; 7 November 1988.	25	17
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113. Savola J-M. Cardiovascular effects of the enantiomers of medetomidine in anaesthetized rats and in pithed rats. Study Report, Farnos Group LTD, Turku, Finland; 7 November 1988.	28	14
126. MacDonald E. Effect of MPV-1440 alone and combined with prazosin on the behaviour, depth of sedation and changes in the levels and turnover rates of brain biogenic amines in rats. University of Kuopio; 7 November 1988. Department of Pharmacology and Toxicology, University of Kuopio, Kuopio, Finland.	28	160
131. Savola J-M. Potentiation of barbiturate-sleep by	28	217

NDA 21-038

enantiomers of medetomidine in the rat. Orion-Farmos
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169. Virtanen R. Evaluation of the (12-adrenoceptor activity and selectivity of the enantiomers of medetomidine. Research Report, Farnos Group LTD, Research Center; 6 October 1987.	30	83
173. Virtanen R. Specificity of dexmedetomidine at the receptor level; in vitro effects in selected isolated organ preparations. Research Report, Farnos Group LTD, Research Center; 7 November 1988.	30	128
174. Hietalaj. The interactions of medetomidine stereoisomers and atipamezole with central D- 1 dopamine receptors. Research Report, 7 November 1988.	30	134
211. Hirsimaki P. Subacute Toxicity Study of Dexmedetomidine (MPV- 1440) by Daily Subcutaneous Administration to Rats for 28 days. Farnos Group LTD, Research Center, TOX 88-013, 1989.	32	147
214. Harling RJ, Burford P, Wrench SM, Buist DP, Crook D, Mullins PA Gøpinath C. MPV-1440. Intravenous Toxicity Study of Dexmedetomidine Hydrochloride in Beagle Dogs. Huntingdon Research Centre, FSG 11/881827, 1991.	35	001
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239. Salonen JS. Pharmacokinetics of 3H-labeled	42	343

NDA 21-038

dexmedetomidine in the rat. Orion-Farmos Study Report;
Study No. BA-88-04. October 1988.

#####

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The following studies were not actually submitted with the NDA 21-038 but were listed (V22/p32). The studies were submitted, upon request, (NDA 21-038 7/06/99 BZ). The two studies included in this review are noted by the assigned review number, (x), below:

Halonen T. Alpha₂-adrenoceptor agonist, dexmedetomidine, protects against kainic acid-induced convulsions and neuronal damage. 31 May 1994.

Jaatinen P. Alleviation of ethanol-induced sympathetic overactivity and neuronal degeneration by dexmedetomidine, a selective α_2 -adrenoceptor agonist. 27 January 1993.

Kaheinen P. Effects of dexmedetomidine and diazepam on isolation induced aggression in mice after repeated administration. 29 September 1989.

[22] Kaheinen P. Effects of dexmedetomidine on uterine contraction in rat. 5 January 1990.

Koulu M. Effects of chronic dexmedetomidine treatment on the metabolism and turnover of catecholamines and indoleamines in discrete brain stem and mesencephalic nuclei in the rat. 7 November 1988.

MacDonald E. Comparison of the effects of the stereoisomers of medetomidine coded MPV-1440 and MPV-1441 on the behavior and levels of brain biogenic amines in adult male rats. 6 October 1987.

Pryor GT, Rebert CS. Effects of medetomidine on spontaneous and evoked brain electrical activity in rhesus monkeys. 31 May 1988.

Ruhioja P. Dexmedetomidine, diazepam and propranolol in the treatment of ethanol withdrawal symptoms: a comparative study. 9 September 1995.

Scheinin H. Effects of MPV-1440 and MPV-1441 on monoamine metabolites in rat CSF. 6 October 1987.

NDA 21-038

Sivenius J. Neuroprotective effects of dexmedetomidine in the gerbil hippocampus following transient ischemia. 15 July 1993.

Viitamaa T. The antipsychotic activities of dexmedetomidine, medetomidine, levo-medetomidine and MPV-295 in the Sidman avoidance test. 7 November 1988.

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**APPEARS THIS WAY
ON ORIGINAL**

NDA 21-038

PHARMACOLOGY

Review
number

NDA
Tab number

[1]

Study Title: Receptogram™ of six compounds (#103)

Study No: E3-9964-01/02/JYG

Vol #27, and page #115:

Conducting laboratory and location: _____

Date of study report: July 1992

Methods: Standard radioligand binding studies, adequately referenced.

Results:

The following tables were copied from the submission (V27/pgs 117, 144, 145):

Table 103-1:

IC₅₀ values of Toremifene, Dexmedetomidine, Atipamezole, MPV-503 A I, MPV-1730 A I and MPV-1743 A III at 5-HT₃ receptors.

5-HT ₃ receptors	IC ₅₀ (M)
Toremifene	
Dexmedetomidine	1 x 10 ⁻⁵
Atipamezole	2.5 x 10 ⁻⁵
MPV-503 A I	> 10 ⁻⁵
MPV-1730 A I	4.9 x 10 ⁻⁶
MPV-1743 A III	1 x 10 ⁻⁷

Table 103-2:

IC₅₀ values of Toremifene, Dexmedetomidine, and Atipamezole, for 40 receptors.

Receptors	IC ₅₀ (M)		
	Toremifene	Dexmedetomidine	Atipamezole
Ion channels			
Chloride Ionophore	> 10 ⁻⁵	> 10 ⁻⁵	> 10 ⁻⁵
Calcium channel T+L	> 10 ⁻⁵	> 10 ⁻⁵	> 10 ⁻⁵
Calcium channel N	> 10 ⁻⁵	> 10 ⁻⁵	> 10 ⁻⁵
Sodium channel	5.0 x 10 ⁻⁶	> 10 ⁻⁵	> 10 ⁻⁵
Potassium channel	> 10 ⁻⁵	> 10 ⁻⁵	> 10 ⁻⁵
Regulatory sites			
Glycine	> 10 ⁻⁵	> 10 ⁻⁵	> 10 ⁻⁵
MK-801	> 10 ⁻⁵	> 10 ⁻⁵	> 10 ⁻⁵
Sigma	4.6 x 10 ⁻⁷	5.0 x 10 ⁻⁶ 4.3 x 10 ⁻⁶	
Uptake sites			
Dopamine uptake	5.0 x 10 ⁻⁶	> 10 ⁻⁵	8.4 x 10 ⁻⁶

NDA 21-038

5-HT uptake	> 10 ⁻⁵	> 10 ⁻⁵	1.3 x 10 ⁻⁶
Norepinephrine uptake	> 10 ⁻⁵	> 10 ⁻⁵	> 10 ⁻⁵

Table 103-2: cont.

IC₅₀ values of Toremifene, Dexmedetomidine, Atipamezole, for 40 receptors.

Receptors	Toremifene	IC ₅₀ (M) Dexmedetomidine	Atipamezole
Neurotransmitter receptors			
Adenosine A ₁	> 10 ⁻⁵	>10 ⁻⁵	>10 ⁻⁵
Adenosine A ₂	> 10 ⁻⁵	>10 ⁻⁵	>10 ⁻⁵
Adrenergic α _{1A}	> 10 ⁻⁵	3.8 x 10 ⁻⁷	1.3 x 10 ⁻⁶
Adrenergic α _{1B}	>10 ⁻⁵	6.8 x 10 ⁻⁷	6.5 x 10 ⁻⁶
Adrenergic β ₁	> 10 ⁻⁵	>10 ⁻⁵	> 10 ⁻⁵
Adrenergic β ₂	>10 ⁻⁵	>10 ⁻⁵	> 10 ⁻⁵
Dopaminergic D ₁	> 10 ⁻⁵	>10 ⁻⁵	> 10 ⁻⁵
Dopaminergic D ₂	> 10 ⁻⁵	> 10 ⁻⁵	> 10 ⁻⁵
GABA _A	> 10 ⁻⁵	> 10 ⁻⁵	> 10 ⁻⁵
GABA _B	> 10 ⁻⁵	>10 ⁻⁵	>10 ⁻⁵
Histaminergic H ₁	> 10 ⁻⁵	> 10 ⁻⁵	> 10 ⁻⁵
Histaminergic H ₂	3.0 x 10 ⁻⁶	>10 ⁻⁵	> 10 ⁻⁵
Histaminergic H ₃	> 10 ⁻⁵	>10 ⁻⁵	5.4 x 10 ⁻⁷
5-HT _{1A}	>10 ⁻⁵	2.1 x 10 ⁻⁶	> 10 ⁻⁵
5-HT _{1B}	>10 ⁻⁵	>10 ⁻⁵	> 10 ⁻⁵
5-HT _{1C}	>10 ⁻⁵	7.0 x 10 ⁻⁶	>10 ⁻⁵
5-HT _{1D}	> 10 ⁻⁵	6.3 x 10 ⁻⁶	> 10 ⁻⁵
5-HT ₂	> 10 ⁻⁵	> 10 ⁻⁵	> 10 ⁻⁵
5-HT ₃	5.3 x 10 ⁻⁸ *	<10 ⁻⁷ *	< 10 ⁻⁷ *
Muscarinic M ₁	>10 ⁻⁵	> 10 ⁻⁵	3.7 x 10 ⁻⁶
Muscarinic M ₂	> 10 ⁻⁵	>10 ⁻⁵	> 10 ⁻⁵
Muscarinic M ₃	> 10 ⁻⁵	>10 ⁻⁵	> 10 ⁻⁵
Nicotinic	>10 ⁻⁵	> 10 ⁻⁵	> 10 ⁻⁵
NMDA	> 10 ⁻⁵	> 10 ⁻⁵	>10 ⁻⁵
Kainate	>10 ⁻⁵	> 10 ⁻⁵	>10 ⁻⁵
AMPA	>10 ⁻⁵	> 10 ⁻⁵	> 10 ⁻⁵
Peptidergic receptors			
Opiate mu	>10 ⁻⁵	>10 ⁻⁵ not	> 10 ⁻⁵
Opiate delta	>10 ⁻⁵	>10 ⁻⁵	> 10 ⁻⁵
Opiate kappa	>10 ⁻⁵	>10 ⁻⁵	> 10 ⁻⁵

* non-specific binding displacement

Summary:

Dexmedetomidine has moderate affinity for the 5-HT_{1A} (3 x 10⁻⁶), 5-HT_{1C} (7 x 10⁻⁶), 5-HT_{1D} (6,3 x 10⁻⁶) and less for 5-HT₃ receptors (1 x 10⁻⁵). The high affinity for the 5-HT₃ receptor in above table was said to be erroneous in a letter accompanying the report and is presented above in the first table. The high affinity was for the adrenergic α_{1A} (3.8 x 10⁻⁷) and α_{1B} (6.8 x 10⁻⁷). The activity of dexmedetomidine at the α₂ site was previously reviewed, see attached review.

#####

NDA 21-038

[2]

Study Title: Dexmedetomidine: affinity and activity on alpha₂-adrenoceptor subtypes (#104)

Study No: not cited

Vol #27, and page #272:

Conducting laboratory and location: Orion Corporation; Orion-Pharma Receptor Laboratory

Date of study initiation: June 1992

Methods: The binding of dexmedetomidine was studied in receptor binding assays and agonist activity was evaluated by the ability of dexmedetomidine to inhibit forskolin-stimulated cAMP accumulation.

Results:

The following tables were copied from the submission (V27/pg. 274, 276):

Table 104-1:

Binding affinities of dexmedetomidine on human alpha₂-adrenoceptor subtypes.

Data is presented as means ± SEM of K_i (in nM), n=3 or 4

<u>Compound</u>	<u>α_{2A}</u>	<u>α_{2B}</u>	<u>α_{2C}</u>
dexmedetomidine	6.2 ± 2.4	4.0 ± 0.3	6.0 ± 0.6

Table 104-2

α_{2A} activity of dexmedetomidine in S115-C10 cells

<u>Compound</u>	<u>max. effect</u> <u>% inhibition</u>	<u>IC₅₀</u> <u>(nM)</u>	<u>95% conf. interval</u> <u>IC₅₀ (nM)</u>	<u>n</u>
dexmedetomidine	82	6.6	4.1 - 10.7	4
adrenaline	82.	89	30 - 260	12

Table 104-3:

α_{2B} activity of dexmedetomidine in NG105-15 cells

<u>Compound</u>	<u>max. effect</u> <u>% inhibition</u>	<u>IC₅₀</u> <u>(nM)</u>	<u>95% conf. interval</u> <u>IC₅₀ (nM)</u>	<u>n</u>
dexmedetomidine	39	6.9	3.6 - 13.2	8
adrenaline	49.	548	390 - 770	10

Table 104-4:

α_{2C} activity of dexmedetomidine in S115-C4 cells

<u>Compound</u>	<u>max. effect</u> <u>% inhibition</u>	<u>IC₅₀</u> <u>(nM)</u>	<u>95% conf. interval</u> <u>IC₅₀ (nM)</u>	<u>n</u>
dexmedetomidine	73	4.0	1.6 - 10.2	3
UK-14304	74.	110	36 - 345	3

Summary:

NDA 21-038

The binding and agonist activity was very potent, but no separation of agonist activity was observed between any alpha₂ sub-types.

#####

[3]

Study Title: The effects of dexmedetomidine N-glucuronides
on alpha-2 adrenoceptors *in vitro* and *in vivo*

(#162)

Study No: CN597122100010

Vol #30, and page #001:

Conducting laboratory and location: _____

Date of study report: August 1997

GLP compliance: not stated

QA- Reports Yes () No (X):

Methods: Alpha₂ agonist activity was studied in:

- 1) *In vitro* guinea pig ileum preparation: standard procedures with electrical stimulation and transducer-polygraph measurement of contractions; dexmedetomidine and the two N-glucuronides, G-DEX1 and G-DEX2 2 were examined along with the alpha-2 antagonist atipametazole (ATI).
- 2) *In vitro* rat vas deferens preparation: standard procedures with electrical stimulation and transducer-polygraph measurement of contractions; dexmedetomidine and the two N-glucuronides, G-DEX1 and G-DEX2 2 were examined along with the alpha-2 antagonist atipametazole
- 3) *In vivo* induction of mydriasis in anesthetized rats: pupil diameter and response was measured in anesthetized rats upon iv administration of drugs.
- 4) *In situ* cardiovascular effects in pithed rats: cardiovascular events were recorded by Polygraph from pithed, atropinized rats. Test compounds were given by iv injections. Tachycardia was produced by electrical stimulation and compared with the effects obtained at the beginning of the study.

Results:

- 1) *In vitro* guinea pig ileum preparation: Dexmedetomidine and the glucuronides were able to inhibit the electrically evoked contractions and this was blocked with both glucuronides by the presence of ATI the antagonist. The 50% inhibition concentrations were approximately 3 orders of magnitude greater for the glucuronides.

NDA 21-038

2) *In vitro* rat vas deferens preparation: As with the guinea pig ileum, dexmedetomidine and both glucuronides were able to inhibit the electrically evoked contractions and this was blocked with glucuronide G-DEX2 by the presence of ATI the antagonist. As approximated from the graphs submitted, the inhibitory effects, the alpha-2 agonist effects of the N-glucuronides, were from 10 to 50 fold less than with dexmedetomidine. No data table available.

3) *In vivo* induction of mydriasis in anesthetized rats: Dexmedetomidine induced mydriasis in doses from 3ug/kg to a plateau between 10 and 30 ug/kg. The glucuronides were both inactive from 10 to 300 ug/kg.

4) *In situ* cardiovascular effects in pithed rats: The inhibition of the electrically induced tachycardia and the vasopressor response of dexmedetomidine, above 1 nmol/kg, was not observed with either glucuronide (G-DEX1 to 10 nmol/kg and G-DEX2 to 1000 nmol/kg).

Summary:

The alpha-2 agonist activity was observed *in vitro*, with dexmedetomidine and the N-glucuronide metabolites in electrically stimulated guinea pig ileum and rat vas deferens preparations, although both were at least one order of magnitude less potent. *In vivo*, the mydriatic response to dexmedetomidine, and the vasopressor effect in pithed rats both metabolites were inactive at doses 100 times greater than the active dexmedetomidine dose.

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[4]

Study Title: Dexmedetomidine does not inhibit the activity of
rat brain monoamine oxidase *in vitro*

(#127)

Study No: unknown

Vol #28, and page #197:

Conducting laboratory and location: _____

Date of study report: November 1989

GLP compliance: no

QA- Reports Yes () No (x):

Methods: Rat brain homogenates were incubated in dexmedetomidine solution of 1, 10 and 100 nM, 1, 10 and 100 uM and 1 mM or 1 mM pargyline for 10 minutes. The C¹⁴-labeled 5-HT was the substrate added and measured.

NDA 21-038

Results:

The pargyline completely inhibited MAO-A at 1mM and dexmedetomidine produced a 16% inhibition at that dose. However, there was no inhibition at any lower doses.

Summary:

Dexmedetomidine is not a MAO-A inhibitor at physiological concentrations. ✓

See Safety Pharmacology and Overall Pharmacology Summary for efficacy data on the sedative effects of dexmedetomidine in mice, rats and dogs.

#####

SAFETY PHARMACOLOGY

[5]

Study Title: The metabolic effects of dexmedetomidine

(#84)

Study No: not stated

Vol #26, and page #220:

Conducting laboratory and location: _____

Date of study initiation: January 1989

Methods: Dexmedetomidine was tested *in vivo* with male Sprague Dawley rats and *in vitro* with fat cells from male golden hamsters. Fed rats were injected sc with dexmedetomidine and 45 minutes later the blood was sampled for Free Fatty Acids, FFA. Another group of fed rats was injected with 30 ug/kg of dexmedetomidine and blood samples from the tail vein were collected at various intervals to measure the time course of plasma glucose. Glucose was measured enzymatically and insulin was measured by a radioimmunological kit.

The fat cells were isolated and the tissue mixed with theophylline to stimulate lipolysis. Dexmedetomidine was added in concentrations of 10^{-8} , 10^{-7} , 10^{-6} M.

Drug, lot#: dexmedetomidine batch S.OT-3841

NDA 21-038

Results:

In fed rats, the subcutaneous administration of dexmedetomidine was examined for effects on blood glucose and immunoreactive insulin (IRI) and serum free fatty acids (FFA). The following table was copied from the submission (V26/p227), and presents the dose response at 45 minutes postdosing:

Dexmedetomidine Dose (ug/kg)	Blood Glucose (nmol/l)	Immuno Reactive Insulin (ng/ml)	Free Fatty Acids (mmol/l)
saline	4.2 ± 0.7	1.4 ± 0.6	0.31 ± 0.08
10	8.6 ± 0.9**	2.2 ± 1.1	0.38 ± 0.08
30	12.3 ± 1.5**	0.9 ± 0.9	0.37 ± 0.13
100	13.8 ± 0.6**	0.1 ± 0.1**	0.37 ± 0.09
300	14.1 ± 1.1**	0.2 ± 0.1**	0.36 ± 0.08

There was a reciprocal dexmedetomidine induced change in blood glucose and IRI. i.e. as the glucose levels increased, the IRI level decreased. Because the rise in glucose appeared at lower doses than IRI decreases, it is probable that the IRI decrease is just a physiological effect of the glucose rise and not a direct inhibition of release by dexmedetomidine. The FFA level was not significantly affected by dexmedetomidine, *in vivo*.

The blood glucose rise was examined over time at the 30 ug/kg dose. The elevation was evident by 15 minutes and peaked around 1 hour. The decline was evident at 2 hours and the blood glucose level returned to control by 6 hours post dosing.

The lipolysis in the fat cells, *in vitro*, was stimulated by theophylline, as measured by glycerol release and dexmedetomidine inhibited the theophylline induced rise in a dose related manner. However, even at the high dose of 10⁻⁶ M, the lipolysis was still higher than with the unstimulated cells.

Summary:

The study demonstrated that dexmedetomidine can increase blood glucose in a dose-dependent fashion and the concomitant fall in blood insulin was seen later in the dose-response curve. There was no effect on serum FFA levels and it is postulated that the glucose rise is through alpha₂-adrenoreceptors. The receptors may be both on pancreatic B-cells and in the CNS, according to the investigators.

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NDA 21-038

[6]

Study Title: A general pharmacology study of dexmedetomidine (DA-9501)

(#122)

Study No: DA-9501; SBL 77-12

Vol #28, and page #82:

Conducting laboratory and location: _____

Date of study report: February, 1996

GLP compliance: _____

QA- Reports Yes () No (X):

Methods: General pharmacology study in male mice, rats and cynomolgus monkeys; in vitro in guinea pig ileum preparation.

Dosing: rats and mice injected iv at 6, 60, and 600 ug/kg; monkeys injected iv at 0.3, 3, and 30 ug/kg

Drug, lot#, and % purity: dexmedetomidine lot# 13-089VII, _____

Formulation/vehicle: normal saline diluent and control

Results:

Mice: 6 / treatment group

6 ug/kg iv = ptosis, slight dec motor activity @ 5min and normal at 1 hr

60 ug/kg iv = ptosis, decreased motor activity, sedation, ataxia, urinary soiling in perineal region; normal after 4 hours.

600 ug/kg iv = slight decrease in motor activity, ataxia, piloerection, bradypnea, urinary soiling in perineal region, 5 minutes to 6 hours post dosing, exophthalmos at 5 min post to 30 min postdosing. Normal after 24 hours.

Thiopental sleeping time:

6 ug/kg, inactive on induction time, but increased duration from 5 minutes to 18 minutes;

60 and 600 ug/kg = decreased latency until sleep note and extended sleeping time from around 5 minutes to more than 3 hours.

Acetic acid induced writhing: 6ug/kg = not active; 60, 600 ug/kg = blocked all writhing

Maximum ECS = no effect at 6, 60, or 600 ug/kg on incidence of tonic convulsions or deaths.

PTZ-induced convulsions = no effect at 6, 60, or 600 ug/kg on incidence of clonic convulsions, onset time or duration

Intestinal transit - charcoal - 60 and 600 ug/kg slowed transit, 6 ug/kg inactive.

Rats: 6/treatment group

NDA 21-038

Effects on body temperature:

6 ug/kg = na;

60 ug/kg = decreased body temperature 30min to 3 hours post;

600 ug/kg = decreased body temperature 15 minutes to 4 hours postdosing. Rebound hyperthermia noted at 24 hours and normal at 48 hours postdosing.

Water and electrolyte balance; 6, 60 and 600 ug/kg induced increased urination and although the molarity decrease, the total sodium and potassium excretion increased.

In vitro guinea pig ileum = at 2×10^{-8} g/ml and above, decreased basal tone, suppression of spontaneous activity, decreased slightly the acetylcholine induced contractions and at 2×10^{-6} . No effect on histamine or barium induced contractions

Cynomolgus Monkeys: iv administration; 3/treatment group. Blood pressure effects:

0.3 ug/kg = significant decrease 10 and 15 minutes postdosing.

3 ug/kg induced a 30% decrease in systolic and diastolic BP at 5 minutes and decrease was significant 5 to 90 minutes postdosing.

30 ug/kg, significant increase in BP immediately after dosing and significant decrease in BP 30 minutes to hours postdosing. Heart rate decreases were parallel to the BP effects.

Femoral blood flow: At 3 ug/kg, significant decrease 5 to 30 minutes post; at 30 ug/kg decrease 5 to 120 minutes postdosing.

Summary:

The data indicated that dexmedetomidine is sedative in mice and can increase the duration of sedation by barbiturate anesthetics without significant effects on either electroshock or pentylenetetrazol induced convulsions. The dexmedetomidine induced intestinal desensitization was observed in vivo in mice and in vitro in a guinea pig ileum preparation. It was shown to decrease body temperature in rats and also acted as a diuretic in this species. The cardiovascular effects of the α_2 -agonist were observed in the monkey as it produced decreased blood pressure, heart rate and femoral blood flow.

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[7]

Study Title: CNS general pharmacology profile in the mouse and the rat (#159)

Study No: D28.1581: Report Number R&D 96/500

Vol #29, and page #155:

Conducting laboratory and location: _____

NDA 21-038

Date of study report: July 1996

Methods: Mice and rats were used in a standard battery of pharmacology tests.

Dosing: The dosing was iv and doses were 1, 3, 10, and 30ug/kg in most tests and included 100, 300, 1000 and 3000 ug/kg in the Irwin behavioral test.

Drug lot#: lot# 295260-0-AX, dissolved in saline

Observations and times: varied by test procedure.

Results:

Mice:

Irwin test : 4/dose

0.001 mg/kg = increased reactivity to touch

0.003 mg/kg = no change

0.01 mg/kg = increased fear, reactivity, abnormal gait, hypothermia, hyperthermia at 24h

0.03 mg/kg = sedation, decreased fear and muscle tone; hypothermia; ptosis

0.1 mg/kg = sedation, decreased fear, muscle tone, reactivity, and respiration; hypothermia

0.3 mg/kg = sedation, decreased fear, muscle tone, reactivity, and respiration;
hypothermia, loss of traction, abnormal gait, jumping, myosis, loss of
corneal reflex

1.0 mg/kg = sedation, decreased fear, muscle tone, reactivity, respiration; hypothermia,
loss of traction, abnormal gait, jumping, myosis, exophthalmos, loss of
corneal reflex, loss of righting reflex

3.0 mg/kg = mortality

Other tests with mice or rats from report (vol29/pgs162-163):

Test Mice - M Rats - R	Dose - (mg/kg) i.v.				Reference Standards	
	0.001	0.003	0.01	0.03	Caffeine 2	cpz* 0.5
Activity Meter - R	-4%	-43%*	-86%***	-94%***	+14%	-57%**
Rotorod - M	+7%	-44%	-43%	-80%		
Barbital sleep time M	+12%	-4%	+30%	+243%***	-40%	+213%**
Ethanol sleep n/10 M	1	0	3	9***		
ECS Threshold M	+11%	+8%	+4%	+11%		
PTZ - latency M	-13%	+4%	+37%	+30%		
Hot plate - latency M	+4%	+29%*	+161%**	+362%***		
Tail-flick - latency R	+7%	+102%**	+188%***	+380%***		
Rectal temp 60 min	+0.2°C	-0.2°C	-0.7°C**	-2.4°C***		

PTZ = pentylenetetrazol

ECS = electroconvulsive shock

* p<0.05

** p<0.01

*** p<0.001

Summary:

Dexmedetomidine was sedative in mice from a dose of 30ug/kg and greater with concomitant reductions in fear, muscle tone, body temperature and decreased reaction to touch at 100ug/kg and higher. Mortality was seen at 3 mg/kg. There was a significant decrease in motor activity in rats at 3 ug/kg and greater and these doses also significantly impaired the rotorod motor coordination in mice. There no were significant anticonvulsant effects by dexmedetomidine against either electroshock or pentylenetetrazol induced convulsions. The analgesic activity was seen in mice on the hot-plate and in the rat tail-flick at 3 ug/kg. The hypothermia in mice was observed at 10 ug/kg.

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[8]

Study Title: The anticonvulsant and anticholinergic effects of dexmedetomidine N₅
(#78)

Vol #26, and page #166:

Conducting laboratory and location: _____

Date of study initiation: March 1989

Methods: A. Pentylenetetrazol induced convulsions; 10 female NMRI mice/treatment group, dosed with saline, dexmedetomidine at 3, 20, 30, 100 or 300 ug/kg or pentobarbitone at 30 or 60 mg/kg ip. Thirty minutes later all mice were injected with pentylenetetrazol, 150 mg/kg sc, and observed for 30 minutes for convulsions and lethality.

B. Tremorine test: 10 female NMRI mice/treatment group, dosed with saline, dexmedetomidine at 3, 20, 30, 100, 300, or 1000 ug/kg or benztropine at 3 mg/kg ip. Thirty minutes later all mice were injected with tremorine, 20 mg/kg ip, and observed for 30 minutes for tremor or convulsions and salivation, the peripheral parasympathomimetic effect of tremorine.

Drug, lot#, and % purity: dexmedetomidine (MPV-1440) HCl, batch S.OT-3841

Results:

The following tables were copied from the submission (V26/pgs 170, 171):

NDA 21-038

Table 078-1

Effect of dexmedetomidine and sodium pentobarbitone on the incidence of pentylenetetrazol-induced convulsions and fatalities in mice. n = 10/group.

Treatment (mg/kg i.p.)	Incidence of convulsions	Death
Saline	10/10	10/10
Dexmedetomidine		
0.003	10/10	9/10
0.01	10/10	9/10
0.03	10/10	8/10
0.1	10/10	9/10
0.3	10/10	8/10
Sodium pentobarbitone		
30	3/10	0/10
60	0/10	0/10

Table 078-2

Effect of dexmedetomidine and benztrapine on the incidence of tremorine-induced effects in mice.

Treatment (mg/kg i.p.)	Incidence of tremor	Incidence of salivation
Saline	10/10	10/10
Dexmedetomidine		
0.01	10/10	10/10
0.03	10/10	10/10
0.1	10/10	10/10
0.3	9/10	10/10
1.0	0/9 1)	9/9 1)
Benztrapine		
3	0/10	0/10

1) one mouse was sick.

Summary:

There was no evidence of anticonvulsant activity by dexmedetomidine and there may have been some central anticholinergic effects only at a very high dose. The tremorine tremors were prevented at the dose of 1000 ug/kg, but not the induced salivation.

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[9]

Study Title: Effect of dexmedetomidine against amygdala-kindled seizures ^{NS}
(#80)

Study No: Not stated

Vol #26, and page #180:

Conducting laboratory and location: _____

NDA 21-038

Date of study initiation: July 1993

Methods: Male Kuo:Wistar rats, 275-325 g, were implanted with bipolar electrodes into the left basolateral nucleus of the amygdala. The implantation was secured to the skull with screws and dental cement. The rats were then stimulated twice daily with current level adjusted to be sufficient to induce afterdischarge. The motor activity was ranked on a scoring scale for convulsion of increasing severity. The rats were considered kindled when they exhibited 3 consecutive class 5 convulsions, jaw and contralateral clonus with rearing and falling.

Dosing: Carbamazepine at 10 and 50 mg/kg(ip), phenytoin 50 mg/kg (ip) and dexmedetomidine at 1 and 5 ug/kg (sc) were injected one hour prior to stimulation in a random order.

A second phase of the experiment, started 3 days after the completion of the part I above. This three day experiment was: 1) rats injected with propylene glycol sc one hour before stimulation. 2) one half injected with carbamazepine at 10 mg/kg ip, and half injected with carbamazepine 10 mg/kg plus dexmedetomidine 5ug/kg sc, one hour before stimulation and 3) the Day 2 groups reversed treatment.

Results:

Dexmedetomidine (1 and 5 ug/kg) and phenytoin (10 and 50 mg/kg) did not attenuate the severity or duration of the convulsions of the pre-kindled rats. Carbamazepine did attenuate the severity of convulsions, in a dose related manner at 10 and 50 mg/kg and the 50 mg/kg also decreased the duration of clonus.

In part 2 of the experiment, dexmedetomidine did not potentiate the antiseizure effects of carbamazepin.

Summary:

In the amygdala kindled seizure model in rats, dexmedetomidine did not have any protective effects at 1 or 5 ug/kg sc and at 5 ug/kg sc dexmedetomidine did not enhance the anticonvulsant effects of carbamazepin.

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[10]

Study Title: Neuroprotection by dexmedetomidine in rat focal ischemia - a comparative study with AMPA and NMDA receptor antagonists.

(#96)

Vol #27, and page #063:

Conducting laboratory and location: _____

Date of study initiation: November 1996

NDA 21-038

Methods: (The protocol was copied from the submission; V27/p066) The Wistar male rats, 275-325 g were used. Anesthesia was initiated by 2-5% halothane (35% oxygen, 62% nitrous oxide). For the operation halothane was reduced to 0.5-1%. Body temperature was maintained at 37°C using a thermoregulatory heating unit () connected to a rectal probe. The left femoral artery was cannulated for continuous monitoring of blood pressure () and for taking blood samples for Pa₀₂, Pa_{CO2} pH () and for blood glucose concentrations ().

Subsequently, the right common carotid artery (CCA) was exposed through a midline ventral cervical incision, and carefully separated from the adjacent sympathetic nerves under a stereomicroscope. The external carotid artery (ECA) was electrocoagulated and a loose ligature was placed around the ECA stump. The CCA was clamped with a microvascular clip. A nylon suture (~ 0.28 mm) was introduced into the ECA and advanced into the internal carotid artery (ICA) until it passed beyond the origin of the middle cerebral artery (MCA). Heparin (40-60 IU) was given to prevent blood coagulation. Reperfusion in the MCA territory was instituted by pulling the suture out after 90 min occlusion. The ECA stump was electrocoagulated and CCA clip was removed.

Drug administration:

Dexmedetomidine (Batch 002,) and CGS-19755 () were dissolved in 0.9% NaCl. NBQX () was dissolved in NaOH and pH was adjusted to 8-8.5 with concentrated HCl. Drugs were infused through a polyethylene catheter inserted into the left femoral vein. Dexmedetomidine was administered as an iv bolus (3ug/kg) over five minutes followed by a 120 min iv infusion, either at a dose of 1ug/kg/h or 3 ug/kg/hr. NBQX was given as an iv bolus (30mg/kg) over 5 min followed by a 120 min iv infusion with a dose of 10 mg/kg/h. CGS-19755 was given as an iv bolus (10mg/kg) over 5 min followed by 120 min iv infusion with a dose of 5 mg/kg/h. Control rats received saline infusions.

Results: (Substantially copied from submission V27/p68)

Physiological variables during MCA occlusion:

There were no differences in blood gases or blood pH between experimental groups and saline controls at baseline, during occlusion and during reperfusion (Table 1). Skull temperature, as measured from the temporalis muscle, was slightly decreased during occlusion in rats given dexmedetomidine (3+3 ug/kg) ($F(1,50)=10.78, p<0.01$). Blood pressure was increased following NBQX as compared to saline controls ($F(1,44)=14.96, P<0.001$). The higher dose of dexmedetomidine (3+3 ug/kg) increased blood glucose concentrations ($F(1,50)=47.75, P<0.001$).

Behavior of animals after MCA occlusion:

Body weight decreased by 14-19% during the 3 day follow-up period. There were no significant differences in weight loss between rats given drug treatment and saline controls. Behavioral scores (a sum of scores from postural reflex test, and forelimb and hindlimb placing) were not different between experimental groups at 24, 48 and, 72 h after MCA occlusion. However, rats receiving NBQX seemed to have only a minor behavioral deficit, but due to high variation, the

NDA 21-038

difference compared to saline controls did not reach statistical significance.

The following table lists the physiological variables measured and the treatment effects after occlusion. The major finding with dexmedetomidine was the significant increase in blood glucose during ischemia and reperfusion. The table was copied from the submission (V27/p70):

Table 96-1:

The effect of drug treatment on various physiological variables in rats during 90 min MCA occlusion

Physiological variables	Saline	NBQX	CGS-19755	Dex (3+1 ug/kg)	Dex (3+3 ug/kg)
Skull temperature, °C					
Baseline	36.5±0.2	36.4±0.5	36.3±0.3	36.3±0.3	36.2±0.6
Ischemia	36.6±0.4	36.3±0.5	36.4±0.3	36.4±0.5	36.0±0.5**
Reperfusion	36.6±0.6	36.3±0.4	36.5±0.3	36.5±0.4	36.4±0.4
Physiological variables					
pO ₂ , mmHg					
Baseline	106±9	105±12	102±11	104±14	112±10
Ischemia	93±0	91±11	93±12	89±17	90±18
Reperfusion	88±1	89±3	83±6	75±13	84±15
pCO ₂ , mmHg					
Baseline	46±10	49±6	49±6	49±9	51±10
Ischemia	46±11	47±6	45±12	40±6	42±9
Reperfusion	42±12	49±6	50±12	40±9	47±9
pH					
Baseline	7.36±0.03	7.37±0.03	7.35±0.03	7.34±0.03	7.34±0.04
Ischemia	7.35±0.02	7.35±0.04	7.33±0.02	7.36±0.03	7.36±0.04
Reperfusion	7.31±0.03	7.33±0.04	7.28±0.03	7.32±0.02	7.31±0.03
MABP, mmHg					
Baseline	91±4	91±4	94±4	97±8	92±5
Ischemia	103±13	114±8*	99±8	95±12	97±8
Reperfusion	84±10	100±7**	85±8	79±11	78±11
B-Glucose, mmol					
Baseline	6.7±0.8	7.0±1.1	6.8±0.5	6.6±1.1	7.3±0.7
Ischemia	5.2±0.5	5.5±0.6	5.6±1.0	6.1±0.8	7.8±1.6***
Reperfusion	5.4±0.7	5.9±0.7	5.5±1.2	5.7±1.0	7.7±1.8***

Values are expressed as mean±SD. Statistical significance as compared to saline group; *P<0.05, **p=0.01, ***p=0.001 (two way ANOVA followed by Student's t-test).

Effect of drug treatment on infarct volume:

The total infarct volume differed between experimental groups in the cortex (F(4,40)=4.17, P<0.01), in the striatum F(4,40)=3.20, P<0.05) and in the cerebral hemisphere (F(4,40)=4.57, P<0.01). Intergroup analyses revealed that NBQX decreased infarct volume by 73% in the cortex (F<0.001) and by 43% in the striatum (F<0.01). The higher dose of dexmedetomidine (3+3 ug/kg) decreased ischemic damage in the cortex p<0.05). When infarct volume was analyzed separately for each coronal slices, the damage was smaller in the cortex following NBQX (F(1,136)=53.61, P<0.001), CGS-19755 (F(1,136)=8.08, P<0.01) and the higher dose of dexmedetomidine (F(1,152)=14.22, P<0.001) than in saline controls. In the striatum, infarct volume was smaller following NBQX (F(1,136) 14.21, P<0.001) and following the higher dose of dexmedetomidine F(1,152)=8.73, P<0.01). The following table was copied from the submission (V27/p75):

Table 96-2

The effect of drug treatment on total infarct volume (mm²) determined from TTC-stained sections 3 days after MCA occlusion

Drug treatment	Hemisphere	Cortex	Striatum
Saline (11)	133.8±51.7	93.2±41.2	40.6±12.5
NBQX (8)	48.3±27.9 (-63.9%)**	24.9±16.0 (-73%)**	23.3±3.6 (-42.6%)*
CGS-19755 (8)	100.4±27.9 (-24.9)	64.2±33.8 (-31.1%)	36.1±8.0 (111%)
Dex (3+1 ug/kg) (8)	124.7±64.5 (-6.8%)	86.0±54.6 (-7.7%)	38.6±12.0 (4.9%)
Dex (3+3ug/kg) (10)	87.1±44.4 (-34.9%)*	56.3±39.7 (-39.6%)*	30.7±10.1 (-24.4%)

Values are expressed as mean±SD. A percentage change compared to saline rats is given in parenthesis. Statistical significance as compared to saline group; *p<0.05, **P<0.01, ***p<0.001 (One-way ANOVA followed by Student's t-test).

Summary:

The neuroprotective effect of dexmedetomidine was compared to the competitive NMDA antagonist CGS-19755 and the AMPA antagonist NBQX. The model system was a brain ischemia damage after 90 minutes of occlusion of the medial carotid artery (MCA). NBQX was the most potent reducer of infarct volume and it significantly raised blood pressure in the rats during administration. The reduction in infarct damage was produced by dexmedetomidine in the cerebral hemispheres and the cortex, but was not significant in the striatum. There were some physiological changes, a very slight reduction in skull temperature with dexmedetomidine and a significant increase in blood glucose.

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NDA 21-038

[11]

Study Title: Neuroprotection by dexmedetomidine in gerbils

N6
(#99)

Study No: Report #17

Vol #27, and page #090:

Conducting laboratory and location:

Date of study report: October 1996

Methods: This study was not actually of neuroprotective effects, as none were measured. This study was to measure physiological parameters affected by dexmedetomidine to find a mechanism that explains the neuroprotective effects observed previously with dexmedetomidine. The anesthetized gerbils has their carotid arteries exposed and clipped closed by aneurysmal clips for 5 minutes. The skull (temporalis muscle) and rectal temperatures were recorded as well as blood gases, pH, mean arterial pressure (MAP) and glucose levels. The animals were maintained in a heating pad at 37°C.

Dosing: The female adult gerbils, 5/group, were injected subcutaneously with dexmedetomidine, 3ug/kg, or saline, 30 minutes prior to carotid occlusion.

Observations and times: Blood gases, pH and glucose were measured before and 30 minutes after dexmedetomidine injection, during carotid occlusion and 30 minutes after reperfusion.

Results:

There were no differences between saline and dexmedetomidine treated animals in blood pH, pO₂, or pCO₂. The blood pressure was insignificantly lower in the dexmedetomidine animals and the blood glucose rose significantly by 68%-83%. There were no significant temperature differences, rectal or skull, between controls and dexmedetomidine treated gerbils. The investigators cite previous literature which reported that hyperglycemia actually increases neuronal damage and because the MAP decreased, they felt that the protection could not be due to better reperfusion. This reviewer agrees if the entire decrease in MAP was due only to decreased heart rate and cardiac output, however some vasodilation could both lower MAP and increase perfusion.

Summary:

The neuroprotective effects of dexmedetomidine in the gerbil carotid occlusion model does not appear to be due to induced changes of stabilization of blood gasses, pH or MAP. There was a 70-80% increase in blood glucose levels but elevated blood glucose has been found to increase rather than decrease ischemic neuronal damage in gerbils.

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NDA 21-038

[12]

Study Title: Effects of dexmedetomidine on motor-coordination and skeletal muscle tone in mice

(NDA tab no.)
(#018)

Vol #24, and page #159:

Conducting laboratory and location:

Date of study report: July 1989.

Methods:

1) Rotorod test: Female NMRI mice, 22-33g, were preselected by a 2 minute practice walk on a revolving horizontal rod. The mice which fell less than twice during the 2 minute training session were used. The mice were injected sc with dexmedetomidine, 10 mice / treatment group, and 30 minutes after injection the mice were placed again on the rotating rod and the number of falls/animal during 2 minutes was recorded.

2) Traction test: Female NMRI mice, 21 - 31g, 10/group. Thirty minutes after sc injection of dexmedetomidine the forepaws of the animals were placed on a horizontal wire and observed to see if it could pull up its body or hindlegs. If this was not accomplished in 30 seconds, muscle relaxation was assumed.

Drug, lot#, and % purity: MPV-1440 HCl, batch S.OT-3841

Results:

The following table was taken from the submission (V24/p163):

Dexmedetomidine dose mg/kg sc	Rotorod number falling	Traction number with muscle relaxation
0	0.2 ± 0.4	0/10
0.001	0.3 ± 0.5	0/10
0.003	0.2 ± 0.4	0/10
0.01	1.0 ± 1.1*	0/10
0.03	2.1 ± 1.5**	0/10
0.1	7.5 ± 3.5**	1/10

* p<0.05

** p<0.01

NDA 21-038

Summary:

The ability to maintain motor coordination sufficient to remain on the rotorod was significantly impaired at 0.01 mg/kg. However the motor strength sufficient to pull their hindlegs up on the wire was not impaired significantly even at the sedative-dose of 0.1 mg/kg.

#####

[13]

Study Title: Treatment of ethanol withdrawal symptoms with subcutaneously administered dexmedetomidine, a selective alpha-2-adrenoceptor agonist

(#151)

Study No: NEFA 94017

Vol #29 and page #065

Conducting laboratory and location: _____

Date of study report: August 1994

Methods: Sixty male Wistar rats; kept intoxicated with intragastric ethanol administrations 3-4 times per day for 4 days. On the fifth day the rats were divided into 4 treatment groups; saline control, dexmedetomidine at 3, 10 and 30 ug/kg/injection.

Dosing: The subcutaneous injections were administered 10, 16, 22 and 39 hours after ethanol withdrawal.

Observations and times: Starting 8 hours after the last ethanol administration and lasting through 58 hours, each rat was rated on four categories of withdrawal on four point scales. The categories were 1) rigidity, 2) intentional tremor, 3) irritability, 4) hypoactivity.

Results:

The investigators found that the sedative effects of dexmedetomidine confounded the "hypoactivity" ratings and statistically evaluated the other 3 categories of ethanol withdrawal. The two higher doses, 10 and 30 ug/kg, significantly reduced the withdrawal symptoms, the overall severity of withdrawal. The analysis of the individual categories only showed significant reductions by the high dose of dexmedetomidine. The statistically significant time points on the three combined categories only numbered 3 of the ten total evaluations. One at the mid dose and two with the high dose group and none were consecutive.

Summary:

Dexmedetomidine significantly reduced ethanol withdrawal symptoms in rats, as seen previously with clonidine.

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NDA 21-038

[14]

Study Title: Treatment of ethanol withdrawal symptoms with dexmedetomidine, ✓
a selective alpha-2-adrenoceptor agonist (#152)

Vol #29, and page #095:

Conducting laboratory and location: _____

Date of study initiation: June 1993

Methods: Thirty-five male Wistar rats; kept intoxicated with intragastric ethanol administrations 3-4 times per day for 4 days. On the fifth day the rats were divided into 2 treatment groups; saline control, dexmedetomidine at 100 ug/kg by gastric intubation 9 and 15 hours after ethanol withdrawal.

Observations and times: Starting 8 hours after the last ethanol administration and lasting through 57 hours, each rat was rated on four categories of withdrawal on four point scales. The categories were 1) rigidity, 2) intentional tremor, 3) irritability, 4) hypoactivity.

The study was done in two parts, the first did the ratings every 3 hours from 8 to 32 hours postdosing and the second part the ratings were from 8 to 57 hours postdosing.

Drug lot#: dexmedetomidine Batch #92E245

Formulation/vehicle: dexmedetomidine was dissolved in distilled water

Results:

This oral dose of 100 ug/kg apparently did not decrease motor activity but there was no significant difference between treatments in the hypoactivity scores or the irritability. However, the overall ANOVA indicated a significant reduction in withdrawal symptoms in rigidity, tremor and the combined rigidity, tremor and irritability scores.

Summary:

Dexmedetomidine, 100 ug/kg po, significantly reduced ethanol withdrawal symptoms.

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[15]

Study Title: The effect of dexmedetomidine on myocardial blood flow, metabolism and mechanical performance during short coronary occlusion and reperfusion in the dog.

In: The effect of dexmedetomidine on the circulation and the normoxic and ischemic heart (#47)

Study No: not stated

Vol #25, and page #099:

Conducting laboratory and location: _____

3.

NDA 21-038

Date of study report: 1991, 1992

Methods: The protocol was copied from the submission with few changes (V25/p101-104)

Study protocol

Nine dogs were used in this protocol, which were premedicated with 200 mcg/kg fentanyl im. Anesthesia was induced by 30 mg/kg thiopental iv. The animals were ventilated with oxygen in nitrous oxide (40%/60%) with 0.5-1.0 % Halothane.

Fifteen minutes and five minutes prior to the coronary occlusion, arterial and local venous blood samples were collected for measurement of blood gases, hemoglobin, oxygen saturation and plasma concentrations of lactate, dexmedetomidine and catecholamines. Cardiac output and all continuously recorded hemodynamic and regional mechanical variables were also determined at these time intervals. After these baseline measurements had been performed, the left anterior descending coronary artery (LAD) was completely occluded during 2 minutes using a tantalum clamp. Regional mechanical variables were determined after 1 minute of occlusion. After release of the occlusion, hemodynamic measurements, blood samples for determination of oxygen saturation and lactate concentration of the local coronary venous blood and regional mechanical variables were determined at reperfusion time 0.5 min, 1 min, 2 min, and 5 min. At each sample time registration of the hemodynamic variables was made just before blood sampling. Local venous blood was continuously withdrawn from start reperfusion to reperfusion time 0.5 min from 0.5 to 1 min, from 1 to 2 min, and from 4 to 5 min. Microspheres for the determination of regional myocardial blood flow were injected immediately after termination of blood sampling at reperfusion time 0.5 min, which coincided with peak reactive hyperemia.

Again, 15 minutes after release of the occlusion, measurements were repeated, followed by administration of 0.1 mcg/kg dexmedetomidine (DM) 15 minutes after dexmedetomidine administration, measurements were repeated following another period of occlusion and reperfusion. This procedure was repeated another 3 times: after dexmedetomidine 1 mcg/kg; after dexmedetomidine 10 mcg/kg and after atipamezole (Ati) 600 mcg/kg.

Results:

Table 47-1:

Hemodynamic data

dose ug/kg	heart rate bpm	MAP	Cardiac Output	LVEDP	dP/dT	SV	SVR
baseline	128 ± 13	78 ± 11	3.4 ± 1.1	4.4 ± 2.6	1647±557	27 ± 8	25 ± 8
dex 0.1	120 ± 15	79 ± 13	3.0 ± 1.0	5.8 ± 4.4	1350±372	25 ± 7	28 ± 9
dex 1.0	96 ± 21*	90 ± 12	2.4 ± 0.9	6.9 ± 4.6	1347±1773	25 ± 5	40 ± 11*
dex 10	81 ± 21*	119 ± 12*	1.4 ± 0.4*	11.5±5.8*	1220±341	18 ± 6*	89 ± 26*
Ati 600	118 ± 22	84 ± 17	3.3 ± 1.5	4.3 ± 3.2	1569±531	27 ± 9	30 ± 13

* p<0.05 from baseline

NDA 21-038

Table 47-2:

Plasma concentrations of dexmedetomidine, the catecholamines and atipamezole

dose ug/kg	dexmedetomidine (ng/ml)	atipamezole (ng/ml)	noradrenaline (nmol/l)	adrenaline (nmol/l)
baseline			0.84±0.64	1.69±1.58
dex 0.1	0.044±0.07		0.70±0.45	1.43±1.01
dex 1.0	0.61±0.19		0.12±0.08*	0.29±0.19*
dex 10	11.8±6.00		0.43±0.18*	0.30±0.10*
Ati 600	2.11±0.74	194±73	1.41±1.13	2.36±1.73

* p<0.05 versus baseline

Summary:

Dexmedetomidine decreased heart rate, contractility and blood flow in the normoxic myocardium. During reactive hyperemia, the epicardial flow was decreased by dexmedetomidine, as in the normoxic heart, but the endocardial flow did not change. The alpha₂-adrenergic coronary vasoconstriction is evidently prevented by metabolic factors related to ischemia. The investigators suggest that the combination of sympatholytic effects and "anti-steal" effects favor the use of dexmedetomidine for myocardia recovery.

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[16]

Study Title: Comparison of the systemic hemodynamic and coronary vascular effects of dexmedetomidine in three animal experimental models.

In: The effect of dexmedetomidine on the circulation and the normoxic and ischemic heart (#49)

Vol #25, page #125:

Conducting laboratory and location:

Date of study report: 1991, 1992

Methods: The methods were copied from the submission with minor changes (V25/p126,127): Seven adult, healthy mongrel dogs weighing between 20 and 40 kg were anesthetized with urethane (CU dogs). They were intubated and ventilated to normocarbina with nitrous oxide 67% in oxygen. Similarly, 7 dogs were anesthetized with sodium thiopental 20 mg/kg iv, intubated

NDA 21-038

and ventilated with nitrous oxide 67% in oxygen and halothane 1%. Fentanyl 2 mg/kg was given iv (HF dogs). 7 adult, healthy goats weighing 30-50 kg were anesthetized with sodium thiopental 20 mg/kg iv. intubated and ventilated with nitrous oxide 67% in oxygen and halothane 1-2% (goats). All animals were instrumented to measure electrocardiogram (ECG), heart rate (HR), mean arterial blood pressure (MAP) and thermodilution cardiac output (CO). Via thoracotomy, an electromagnetic flow probe was placed around the left anterior descending (dogs) or the left circumflex (goats) coronary artery, and a sampling catheter introduced into the accompanying vein. Systemic vascular resistance (SVR) and coronary vascular resistance (CVR) were calculated. During stable hemodynamic conditions, baseline measurements (baseline) were made. Dexmedetomidine (DM) in successive doses of 0.1, 0.3, 1.3 and 10 mcg/kg was infused iv over 2 minutes. For each dose data was collected at peak mean arterial blood pressure effect (1-3 min) and 15 minutes later (recovery).

Results:

The following table is representative of data tables in this submission and presents data from 1 of the 5 doses recorded and 6 of the 14 parameters measured:

- MAP = mean arterial pressure (mmHg)
- HR = heart rate (beats/min)
- CO = cardiac output (l/min)
- SVR = systemic vascular resistance (dynes/sec/cm⁵)
- SVO2 = mixed venous oxygen saturation (%)
- AVO2 = Arterio-venous oxygen saturation (%)

parameter	baseline	1mcg/kg - dexmedetomidine		prazosin	atipamezole
		peak	15 min		
MAP (HF)	99.52#	137.95*	104.86	99.39&	58.06*
MAP (CU)	126.00	143.00	104.67	77.00*	44.33*
MAP goat	103.71	119.57	91.29	47.86*	77.29
HR (HF)	91.06#	64.67*#	72.80*#	82.86	142.95*
HR (CU)	153.67+	105.50*	111.50*#	79.67*	100.17*
HR goat	98.57	84.71	83.43*	64.29*	157.86*
CO (HF)	3.69	2.48*	2.67*	1.98*	2.66
CO (CU)	3.74	2.10*	2.30*	1.41*	2.32
CO goat	3.10	2.53	2.58	1.77*	4.02
SVR (HF)	2569	5010*	3481	4238	1874
SVR (CU)	2751	5621*	3777	4742**	1694