Overall Toxicology Summary

Dextromedetomidine, the dextro isomer of medetomidine, is a potent and selective α_2-agonist with sedative/hypnotic, hypotensive and analgesic effects. The clinical use is to be in the ICU for postoperative sedation and analgesia reducing anesthetic and narcotic analgesic requirements. The α_2-agonist activity reduce adrenergic activation, producing a sympatholytic effect, bradycardia and a reduced cardiovascular response to noxious stimuli.

The administration of dexmedetomidine is by intravenous infusion with maximum total daily doses of less than 20 µg/kg and blood concentrations of less than 30 ng/ml. The maximun recommended human dose (MHRID) is about 17.8 µg/kg/day (0.6919 mg/m^2) and the initial recommended loading dose is 1 µg/kg.

Acute Toxicity

The acute toxicity, after rapid iv bolus injection, mice demonstrated a sex difference and the highest non-lethal dose was 5000 µg/kg in females and 1000 µg/kg in males; 20,000 and 10,000 µg/kg in females and males, respectively, after subcutaneous injections. In rats, the highest non-lethal dose after rapid iv bolus was 1000 µg/kg in both sexes and after subcutaneous injection it was 5000 in males and 1000 µg/kg in females (vol 23/pg 222) Considering 1000 µg/kg was non-lethal in mice and rats after iv injection, the ratio of these doses in mg/m^2 and the daily MRHID (loading dose, 1.0 µg/kg) is 120X and 240X, respectively. In comparison with the MRHID of 17.8 µg/kg for a 24 hour infusion, these non-lethal dose in the mice and rats were still 5X and 9X the human dose on a on mg/m^2 basis. The estimated highest non-lethal dose in dogs was about 1000 µg/kg following rapid intravenous injection and this is approximately 30X the MRHID on mg/m^2 basis.

The clinical signs at high non-lethal doses was the same in both rats and mice; sedation, piloerection, exophthalmia, salivation, tachypnea and clonic convulsions. The signs at lethal doses also included jumping, dyspnea, chromodacyrhea, red urine and red fluid from nose and mouth.

Subacute Toxicity:

The toxicity of repeat-dosing was examined in both rats and dogs in studies 4 weeks in duration with im or iv administration. The rats were tested after sc injection for 4 weeks and after intrathecal administration for 2 weeks. The dogs were tested for 2 weeks of intrathecal adminstration after a single dose pilot study.

The im administration of 20, 100 and 500 µg/kg to rats produced the pharmacological effects of sedation, piloerection and cloudy corneas in a dose related manner. The two high doses also produced exopthalmus and glucosuria and some hypertrophy of the adrenal glomerulosa. The toxicological effects were seen at 100 and 500 µg/kg decreased body weight gain and thymus

weight and dose-related pulmonary perivascular hemosiderin laden macrophages. The high dose males also had decreased weight of testes, seminal vesicles and prostate. The NOAEL was the 20 μg/kg dose. The 4 week sc study in rats used the same doses and produced the same effects although there was an elevated alkaline phosphatase level at 100 and 500 μg/kg and decreased uterine weight at 500. The NOEL was 20 μg/kg in the males and possibly 100 in the females. The intravenous dosing in rats was at 10, 40 and 160 μg/kg and there was still the dose-related pharmacological sedation, piloerection and exopthalmos at the high dose. The glucosuria, corneal opacities and elevated alkaline phosphatase at 40 and 160 and increased liver weight for females the high dose. The 10 μg/kg dose was considered the NOEL. All of these NOELs produced a ratio of less than 1.0 compared to the MHRID in mg/m^2 the daily dose of 17.8 μg/kg/day.

In dogs, the iv study used doses of 10, 50 and 250 μg/kg for 4 weeks. The sedation, ataxia, muscle twitches, miosis and slowed respiration rate were dose related pharmacological effects at all doses. The toxicological signs were seen mainly in the high dose animals, elevated ornithine carbamyl transferase, alkaline phophatase and hepatic apototic bodies and serum GGT level were significantly elevated in both MD and HD groups.. There was some increased liver weight and decreased thymus weight in the lower doses but 10 μg/kg could be considered LOAEL and the ratio with MHRID was 0.3. The im study in dogs used the same doses, 10, 50 and 250μg/kg, but was run once with males and once with females and no pathology reports were supplied for the control and LD animals. The toxicity was similar to the iv study, with elevated alkaline phosphatase, ALT, in the HD males and females and in the MD males. The MD and HD females had eosinophilic inclusions in the hepatocytes. The ALT was over 8-fold in one HD male and the creatinine kinase, aspartate aminotransferase and alaninme amionotransferase were all elevated in the high dose males. The NOEL was 10 μg/kg in both male and female studies. The 50 μg/kg NOEL dose in the iv study provides a ratio of 1.5 with the MHRID in mg/m^2., but the 10 μg/kg dose has a ratio of less than 1. These ratios were in terms of the maximum recommended human dose (MHRID), 17.8 μg/kg/day.

The intrathecal administration of dexmedetomidine in bolus doses of 1.5, 6 and 24 µg/rat for two weeks, produced transient dose-related sedation but no histopathology that was difference from saline controls. The pilot study in two dogs indicated that 40 µg/dog produced transient hindlimb weakness and after 72 µg and 144µg/dog there was a marked decrease in heart rate and increased sedation. The sedation was so profound at 144 µg/dog in 1/2 dogs, that it was not arousable by voice or paw pinch for about one-half hour, starting 20 minutes post-dosing. Dexmedetomidine was administered intrathecally to dogs at the doses of 2, 12 and 80 µg/dog for 28 consecutive days. The 2 µg dose did not produce any observable changes, the 12 µg dose produced some transient sedation and incoordination. There was incoordination was evident in all dogs at the 80 µg/dog dose and some demonstrated analgesia. The was no clinical chemistry, hematology or urinalysis changes attributed to dexmedetomidine. The histopathological changes were all attributed to the invasive procedures as this was also evident in control animals. The 80 µg/dog dose did slightly increase the QT interval in 8/10 dogs and one dog had a 2nd degree AV block. The veterinary

cardiologist determined the QT lengthing was minor and not cardiotoxic events.

The acute toxicity studies indicated that the safety ratio of acute toxicity is at least two orders of magnitude greater than a human would be expected to encounter, when compared to the loading dose of 1.0 μg/kg. However, the the subacute studies are inconclusive. It is recognized that the ratio values with the MHRID are comparing a dose from a total day of infusion in the ICU with a daily bolus dose in the animals. It would be expected that if the study dose had been infused, then the daily dose comparisons would be more relevant. It is not known if the toxicities observed, liver damage, reduced testes and thymus growth and adrenal glomerulosa hypertrophy, would be reduced if the daily dose were presented in a more gradual fashion, infusion.. It is also possible that the extended exposure during infusion, even at lower concentrations, would be more damaginmg as the tissues have less time without exposure, for repair. In addition, the toxicities observed in the animals studies are the results of 4 week of administration is four times the conceived duration and 14 times the presently proposed duration of treatment.

It is the impression of this reviewer that, although the safety ratios in subacute studies are generally less than unity, the extension of the testing to weeks versus the planned 24 hours, greatly exacerbates any drug induced toxicity. This impression is based, in part, to the fact that the acute toxicities produce safety ratios several orders of magnitude greater than 1. In terms of clinical safety, dexmedetomidine, an α_2-agonist, has the following possibly adverse pharmacological actions:

- initial hypertension if rapidly injected as an iv bolus. ? boses
- hyperglycemia - seen in transiently in rats, gerbils and rabbits, but not observed in dog studies
- increased GFR and increased "filtered fraction" - seen transiently in rats and rabbits producing glucouria. In dogs no glucosuria was observed by some increased proteinuria was observed in the dog studies.
- hypothermia has been observed in animal studies, although this is controlled in the ICU setting.

The following toxicology effects have all been seen after repeated administration and have not been observed acutely:

- elevated liver enzymes, enlarged livers and eosinophilic inclusions in hepatocytes and have been observed in rats and dogs and after 250 μg/kg/day in the dog, apototic bodies were also observed. This dose is about 7 fold the MRHID of a daily 17.8 μg/kg, calculated in units of mg/m^2 . ✓
- decreased thymus weight have been observed in rats and dogs and decreased testicular and seminal vesicle weights were observed in rats. ✓
- hypertrophy of the adrenal glomerulsa is observed in both rats and dogs. ✓

Although the ratios of the NOEL in repeated dose dog and rat studies and the MRHID have mostly been below 1, this reviewer feels this was only the result of prolonged adminstration of high bolus doses and do not portend problems at the present recommended duration of treatment. The lack of

toxicology studies using administration by infusion, the clinical use, significantly hinders this evaluation. Another compounding variable is the fact that over 50% of the excreted dexmedetomidine is in the form of metabolites that are not produced in rats or dogs, except for trace amounts. (Metabolic Pathways: pg. 72 (rats), page 100 (human))

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REPRODUCTIVE TOXICOLOGY

[56]

Study title: Fertility study (Segment I study) of Dexmedetomidine in Rats by Subcutaneous Administration. (#228)

Volume# 40, Page#147:
Study No: and number: TOX 89-001
Site and testing facility: [redacted]
Dates: started January 3, 1989, ended August 18, 1989
GLP compliance: yes (Vol 40/pg 183): QA- Reports Yes (Vol 40/ pg 169)
Lot and batch numbers: Batch 14, series 7.1.88
Protocol reviewed by Division: No (X):

Methods:
- Species/strain: Rats / Sprague Dawley [redacted]
- Doses employed: 0, 6 18, 54 µg/kg/day; control, LD, MD, HD, respectively.
- Route of Administration: daily subcutaneous injection
- Study Design: Males were injected for 10 week prior to mating and the mating for 2 weeks prior to necropsy. One half of the females were dosed for 2 weeks prior to mating, during mating, gestation until Day 20 of lactation and then sacrificed. The other half to the females were dosed through gestation and lactation, until day 20 post delivery.

Males: 45 days of age at start, about 210 gm, daily injection for ten weeks prior to mating (71 injections).
Females about 75 days of age at start, mean 215 gm, daily injections for 2 weeks prior to mating, during mating, gestation and lactation until sacrifice.
- Number of animals/sex/dosing group: 24 males and 24 females/ dose group

Parameters and endpoints evaluated:. Body weights weekly, food and water consumption weekly, clinical signs and mortality daily.
-At necropsy, uterine content and corpora lutea on Day 20 of gestation with one-half of dams and the remaining half at Day 20 of lactation. Viability and weight of young on days 1, 4, 14 and 21 postnatal.

Results: Males
- Clinical signs: sedation and piloerection, dose related
- Mortality: No mortality during study.

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