To prepare the infusion, withdraw 2 mL of dexmedetomidine hydrochloride injection, and add to 48 mL of 0.9% sodium chloride injection.

2.4 Preparation of Solution

Dexmedetomidine hydrochloride injection must be diluted with 0.9% sodium chloride injection to achieve required concentration.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and vial contents are intact and container closure has not been tampered with.

Dexmedetomidine has been shown to be incompatible when administered with the following drugs: amphotericin B, ceftriaxone, cefotaxime, cephalosporins, ciprofloxacin, dobutamine, dopamine, fentanyl, haloperidol, lidocaine, milrinone, midazolam, morphine, nitroglycerin, norepinephrine, propofol, and ramipril.

Dexmedetomidine hydrochloride injection dosing should be individualized and titrated to desired clinical response.

For patients over 65 years of age, dosage adjustments should be made based on age, co-morbidities, concurrent medications, and other factors. Clinical judgment should be exercised when dosing is performed in this population.

Hypertension was defined in absolute and relative terms as systolic blood pressure of ≥100 mmHg or ≥25% lower than post-study drug infusion value. Respiratory depression was defined in absolute and relative terms as respiratory rate (RR) of ≥8 per minute or ≥25% lower than post-study drug infusion value. Bradycardia was defined in absolute and relative terms as a heart rate of <40 beats per minute or <30% lower than post-study drug infusion value. Blood pressure was defined in absolute and relative terms as diastolic blood pressure of ≤55 mmHg or ≥30% lower than post-study drug infusion value. Hypoglycemia was defined as a glucose level of <70 mg/dL. Anemia was defined as a hemoglobin level of <10 g/dL. Leukopenia was defined as a white blood cell count of <4,000 cells/mm³. Transient hypertension has generally not been necessary, although reduction in loading infusion rate may be considered in patients with hypertension and impaired renal function.

Some patients receiving dexmedetomidine have been observed to be arousable and alert when stimulated. This alone should not be considered as evidence of lack of efficacy in the absence of other clinical signs and symptoms.

6.4 Adverse Reactions

5.2 Hypotension, Bradycardia, and Sinus Arrest

Hypotension and bradycardia were the most common adverse reactions associated with the use of dexmedetomidine hydrochloride. In clinical trials, the most common adverse reactions associated with the use of dexmedetomidine hydrochloride were hypotension, bradycardia, and sinus arrest. Other reported adverse reactions included transient hypertension, hypoglycemia, hypoventilation, visual disorders, and headache. In clinical trials, the most common adverse reaction was hypotension, which was observed in 37% of patients receiving dexmedetomidine hydrochloride. In post-marketing surveillance, the most common adverse reactions observed were hypotension, bradycardia, and sinus arrest.

5.4 Pharmacokinetics

Dexmedetomidine is a potent alpha2-adrenergic agonist indicated for:

Dexmedetomidine Hydrochloride Injection 200 mcg doses ranging from 0.2 to 1 mcg/kg/h for 24 hours. Initial U.S. Approval: 1999 For intravenous use

11 DESCRIPTION

Table 3: Adverse Reactions Experienced During Post-approval Use of Dexmedetomidine Hydrochloride

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>37%</td>
</tr>
<tr>
<td>Bradycardia</td>
<td>3%</td>
</tr>
<tr>
<td>Sinus Arrest</td>
<td>4%</td>
</tr>
<tr>
<td>Transient hypertension</td>
<td>3%</td>
</tr>
<tr>
<td>Hypoglycemia</td>
<td>4%</td>
</tr>
<tr>
<td>Anemia</td>
<td>3%</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>4%</td>
</tr>
</tbody>
</table>

4.2 Common adverse reactions:

A. Transient hypertension

In one study of 10 healthy adult volunteers, administration of dexmedetomidine hydrochloride injection for 45 minutes at a plasma concentration of 0.4 μg/mL resulted in a decrease in mean arterial pressure (MAP) of 18% and a decrease in heart rate of 38%. In another study, administration of dexmedetomidine hydrochloride injection for 60 minutes at a plasma concentration of 0.5 μg/mL resulted in a decrease in MAP of 22% and a decrease in heart rate of 39%.

B. Bradycardia

Bradycardia was defined in absolute and relative terms as <40 beats per minute or <30% lower than pre-study drug infusion value.

C. Hypoglycemia

Hypoglycemia was defined as a glucose level of <70 mg/dL.

D. Hypotension

Hypotension was defined in absolute and relative terms as systolic blood pressure of ≥100 mmHg or ≥25% lower than post-study drug infusion value.

E. Anemia

Anemia was defined as a hemoglobin level of <10 g/dL.

F. Leukopenia

Leukopenia was defined as a white blood cell count of <4,000 cells/mm³.

5.3 Administration

Dexmedetomidine hydrochloride injection should be administered at a rate not to exceed 100 μg/min.

Dexmedetomidine hydrochloride has been shown to be incompatible with the following intravenous fluids: dextrose 5% in water, lactated Ringer’s solution, normal saline, and 0.9% sodium chloride injection.

Dexmedetomidine hydrochloride injection should be administered at a rate not to exceed 100 μg/min.

Dexmedetomidine hydrochloride injection should be administered at a rate not to exceed 100 μg/min.
Dexmedetomidine hydrochloride is the S-enantiomer of medetomidine and is chemically described as (+)-4-(S)-[1-(2,3-dimethylphenyl)-4-piperidinyl]methyl]-2,3-dimethyl-6-oxo-1,6-dihydropyridine-1-carboxylic acid (salt form with sodium). Dexmedetomidine hydrochloride is available in two strengths: 1 mcg/kg/hr and 2.2 mcg/kg/hr, in 2 mL vials. The solution is preservative-free and contains no additives.

**PHARMACOKINETICS**

The loading doses for each of the above indicated groups were 0.5, 0.5, 1 and 2.2 mcg/kg, respectively. The steady-state volume of distribution (Vss) of dexmedetomidine was approximately 118 liters. Dexmedetomidine protein binding was approximately 99%. The terminal elimination half-life (t1/2) of dexmedetomidine is approximately 2 hours and clearance is estimated to be approximately 39.4 L/hr.

**Drug Metabolism**

Dexmedetomidine undergoes almost complete biotransformation with very little unchanged dexmedetomidine excreted in urine and metabolites are found in both urine and feces. Biotransformation involves both direct glucuronidation as well as cytochrome P450 mediated metabolism. The major metabolic pathway is the production of 3-hydroxy N-methyl-dexmedetomidine, 3-carboxy N-methyl-dexmedetomidine, and N methyl O glucuronide. These N-methyl and O-glucuronide metabolites are also excreted in both urine and feces. Approximately 85% of the radioactivity recovered in the urine is accounted for by these two metabolites with approximately 44% recoverable as the glucuronide metabolites. The terminal elimination half-life (t1/2) of these metabolites is approximately 2 hours.

The total body clearance (CL) for the unchanged dexmedetomidine is approximately 25.8 L/hr and clearance for total radioactivity accounted for is approximately 28.9 L/hr. This clearance value was based on the assumption that 100% of the administered radioactivity was recovered in the urine. Following intravenous administration, dexmedetomidine exhibits the following pharmacokinetic parameters: a rapid distribution phase resulting in a peak plasma concentration (Cmax) of approximately 1.4 ng/mL within approximately 3 minutes and followed by a fixed maintenance infusion of 0.7 mcg/kg/hr. After achieving the desired level of sedation, topicalization reduces the infusion rate of dexmedetomidine to 0.4 mcg/kg/hr.

**Pharmacodynamic and Clinical Effects**

Dexmedetomidine hydrochloride is a short-acting alpha 2-adrenergic agonist with a rapid onset of action (2-3 minutes) that may be titrated from 0.25 to 2 mcg/kg/hr. The maximum recommended dose is 2 mcg/kg/hr. Dexmedetomidine is indicated in adults for the sedation of non-intubated, non-ventilated patients requiring sedation for procedures in which patients can tolerate spontaneous ventilation. Although dexmedetomidine hydrochloride is dosed to effect, it may be necessary to consider dose reduction in patients with renal or hepatic impairment (see Table 8). The sedative effects of dexmedetomidine were evaluated by comparing the percent of patients not requiring rescue naloxone to achieve a specified level of sedation using the standard Observer's Assessment of Sedation Scale (OAA/S) (see Table 1).

The safety of dexmedetomidine hydrochloride in patients with severe renal impairment (creatinine clearance: <30 mL/min) compared to healthy subjects.

**8.2 Labor and Delivery**

The safety and efficacy of dexmedetomidine hydrochloride for sedation during labor and delivery have not been studied. The safety of dexmedetomidine hydrochloride in pregnant patients has not been studied. Therefore, the use of dexmedetomidine hydrochloride in pregnant patients is not recommended (see Table 7). There were no differences in the adverse cardiac or respiratory events (5% of patients) observed in second generation offspring.

**13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

Fertility in male or female rats was not affected after daily subcutaneous injections of dexmedetomidine at doses up to 54 mcg/kg (less than the maximum recommended human intravenous dose on a mcg/m2 basis) administered from 10 weeks prior to mating in males, and from mating to weaning in females (see Table 6). Genotoxicity studies revealed that dexmedetomidine was not clastogenic in the mouse bone marrow micronucleus assay, the mouse lymphoma forward mutation assay with, but not without, rat S9 metabolic activation. In contrast, dexmedetomidine was not mutagenic in the Ames test with, but not without, rat S9 metabolic activation. Dexmedetomidine was not carcinogenic in the mouse bioassay. However, several generations of mice exposed to intravenous dexmedetomidine at doses up to 10 mg/kg (less than the maximum recommended human intravenous dose on a mcg/m2 basis) administered from 10 weeks prior to mating in males, and from mating to weaning in females.

**14.1 CLINICAL STUDIES**

The safety and efficacy of dexmedetomidine hydrochloride injection has been established in two randomized, double-blind, placebo-control

**16.1 PRECAUTIONS TO AVOID ACUTE RESPIRATORY DEPRESSION**

A reduction in the maintenance infusion should be considered for patients greater than 65 years of age.

**18.1 REACTIONS TO INSUFFICIENCY**

The reduction in the maintenance infusion should be considered for patients greater than 65 years of age.