

Data Sheet

0.5% Marcain[®] DENTAL with Adrenaline 1:200,000

bupivacaine hydrochloride 0.5% with adrenaline 1:200 000.

Presentation

0.5% Marcain[®] DENTAL with Adrenaline 1:200,000 is a clear, colourless, sterile, particle-free, isotonic aqueous solution. It contains sodium metabisulphite as an antioxidant. The pH of the solution is 3.3-5.0. 0.5% Marcain[®] DENTAL with Adrenaline 1:200,000 is paraben-free and for single use only. Remaining unused contents should be discarded.

Uses

Actions

Bupivacaine like other local anaesthetics, causes a reversible blockade of impulse propagation along nerve fibres by preventing the inward movement of sodium ions through the nerve membrane. Local anaesthetics of the amide type are thought to act within the sodium channels of the nerve membrane.

Local anaesthetic medicines may have similar effects on excitable membranes in the brain and myocardium. If excessive amounts of medicine reach the systemic circulation rapidly, symptoms and signs of toxicity will appear, emanating mainly from the central nervous and cardiovascular systems.

Central nervous system toxicity usually precedes the cardiovascular effects as it occurs at lower plasma concentrations. Direct effects of local anaesthetics on the heart include slow conduction, negative inotropism and eventually cardiac arrest.

The addition of a vasoconstrictor such as adrenaline may decrease the rate of absorption of bupivacaine.

Pharmacokinetics

Bupivacaine is a long-acting, amide-type local anaesthetic chemically related to lignocaine and mepivacaine. It is approximately four times as potent as lignocaine. The onset of the blockade is slower than with lignocaine, especially when anaesthetising large nerves.

Bupivacaine has a pKa of 8.1 and is extensively bound to plasma proteins. Bupivacaine exhibits a high degree of lipid solubility with an oil/water partition coefficient of 27.5. These factors contribute to its prolonged duration of action.

The onset of action following dental injections is usually 2-10 minutes and anaesthesia may last two or three times longer than with lignocaine or mepivacaine for dental use, in many patients up to 7 hours. The duration of anaesthetic effect is prolonged by the addition of adrenaline 1:200 000.

The plasma concentration of bupivacaine depends upon the dose, the route of administration and the vascularity of the injection site. Absorption may be slowed by the addition of adrenaline.

Bupivacaine has a total plasma clearance of 0.58 L/min, a volume of distribution at steady state of 73 L, an elimination half-life of 2.7 h and an intermediate hepatic extraction ratio of 0.4 following experimental IV administration in adults. The terminal elimination half-life is prolonged in the newborn to approximately 8 hours. In children over 3 months the elimination half-life is similar to that in adults. Bupivacaine is mainly bound to alpha-1-acid glycoprotein in plasma with a plasma binding of 96%.

An increase in alpha-1-acid glycoprotein, which occurs postoperatively after major surgery, may cause an increase in the total plasma concentration of bupivacaine. The level of free medicine will remain the same. This explains why total plasma concentrations above the apparent toxic threshold level of 2.6-3.0 mg/L are well tolerated.

Following IV administration bupivacaine is excreted in the urine principally as metabolites with about 6% as unchanged medicine.

Various pharmacokinetic parameters can be significantly altered by a number of factors including the presence of hepatic and renal disease, route of administration, age of the patient and certain concomitant medication.

Indications

0.5% Marcain® DENTAL with Adrenaline 1:200,000 is indicated for the production of local anaesthesia in routine dental procedures and oral surgery by means of infiltration and nerve block techniques.

Dosage and Administration

As with all local anaesthetics, the dosage varies and depends upon the area to be anaesthetised, the vascularity of the tissues, the number of neuronal segments to be blocked, individual tolerance and the technique of anaesthesia and the physical condition of the patient.

The lowest dosage that results in effective anaesthesia should be used. For specific techniques and procedures refer to standard textbooks.

The 0.5% concentration with adrenaline is recommended for infiltration and block injection in the maxillary and mandibular area when a longer duration of local anaesthetic action is desired such as for oral surgical procedures generally associated with significant postoperative pain. The average dose 2.2 mL (11 mg) per injection site will usually suffice. An occasional second dose of 2.2 mL (11 mg) may be used if necessary to produce adequate anaesthesia after making allowance for 2 to 10 minutes onset time (see Pharmacokinetics).

The lowest effective dose should be employed and time should be allowed between injections. It is recommended that the total dose for all injection sites, spread out over a single dental sitting should not ordinarily exceed 90 mg for a healthy adult patient (8 x 2.2 mL cartridges of 0.5% Marcain® DENTAL with Adrenaline 1:200,000). Injections should be made slowly and with frequent aspirations.

Note:

1. Toxic doses vary widely between patients and toxic effects may occur after any local anaesthetic procedure. Careful observation of the patient must therefore be maintained. The dose administered must be tailored to the individual patient and procedure, and the maximum dose quoted should be used as a guide only.
2. The safe dose for people with acute or chronic disease, especially those on medication, may be substantially less.

3. The rapid injection of a large volume of local anaesthetic solution should be avoided and fractional doses should be used where feasible. For most of the indications the duration of 0.5% Marcain[®] DENTAL with Adrenaline 1:200,000 is such that a single dose is sufficient.
4. Injection of repeated doses of bupivacaine may cause significant increase in blood levels with each repeated dose, due to accumulation of the drug or its metabolites, or due to slow metabolic degradation.

Paediatrics

0.5% Marcain[®] DENTAL with Adrenaline 1:200,000 in dentistry cannot be recommended for children younger than 12 years of age. A reduced dosage based on body weight and surface area should be used. The dosage should be calculated for each patient individually and modified in accordance with the dentist's experience and knowledge of the patient.

Use in debilitated or elderly patients

Debilitated or elderly patients, including those with partial or complete heart block, advanced liver disease or severe renal dysfunction should be given a reduced dosage commensurate with their physical condition (see WARNINGS AND PRECAUTIONS).

Contraindications

Absolute

1. Allergy or hypersensitivity to amide type local anaesthetics or sodium metabisulphite in adrenaline-containing solutions. Detection of suspected hypersensitivity by skin testing is of limited value.
2. Local anaesthetic techniques must not be used when there is inflammation and/or sepsis in the region of the proposed injection.
3. Intravenous administration.
4. Adrenaline is contraindicated in conditions where the production or exacerbation of tachycardia could prove fatal, such as thyrotoxicosis or severe heart disease.
5. Solutions containing adrenaline should not be used in patients with a known sensitivity to sympathomimetic amines.
6. Solutions with adrenaline should not be used in most patients with cerebral arteriosclerosis.

Warnings and Precautions

1. When any local anaesthetic agent is used, resuscitative equipment and medicines, including oxygen, should be immediately available to manage possible adverse reactions involving the cardiovascular, respiratory or central nervous systems.
2. Injections should always be made slowly with frequent aspirations to avoid inadvertent intravascular injection, which can produce toxic effects.

3. Careful and constant monitoring of cardiovascular and respiratory vital signs and the patient's state of consciousness should be accomplished after each local anaesthetic injection. It should be kept in mind that at such times restlessness, anxiety, tinnitus, dizziness, blurred vision, tremors, depression or drowsiness may be early warning signs of CNS toxicity.
4. The safety and efficacy of 0.5% Marcain[®] DENTAL with Adrenaline 1:200,000 depend on proper dosage, correct technique and adequate precautions. Standard textbooks should be consulted regarding specific techniques and precautions for various dental anaesthetic procedures.
5. The lowest dosage that results in effective anaesthesia should be used (see Dosage and Administration). Repeated injection of 0.5% Marcain[®] DENTAL with Adrenaline 1:200,000 may cause accumulation of bupivacaine or its metabolites and result in toxic effects. However this is unlikely to occur at the doses normally used in dentistry. Tolerance to elevated blood levels varies with the status of the patient. Debilitated, elderly or young patients, including those with partial or complete conduction block, advanced liver disease or severe renal impairment, should be given reduced doses commensurate with their age and physical condition. Caution should be used when administering bupivacaine to children under 12 years of age.
6. In view of the risk of inadvertent intravascular injection bupivacaine should be given with great caution to patients with epilepsy, severe bradycardia, cardiac conduction disturbances, severe shock or digitalis intoxication. Bupivacaine should also be administered with great caution to patients with impaired cardiovascular function as they may be less able to compensate for functional changes associated with the prolongation of AV conduction produced by these medicines.
7. Local anaesthetics should be given with great caution (if at all) to patients with pre-existing abnormal neurological conditions, e.g. myasthenia gravis.
8. Since bupivacaine is metabolised in the liver and excreted via the kidneys, the possibility of bupivacaine accumulation should be considered in patients with hepatic and/or renal impairment. Patients with hyperthyroidism are also more susceptible to toxicity with bupivacaine.
9. Inadvertent intravascular or subarachnoid injection of small doses of local anaesthetics injected into the head and neck area, including retrobulbar, dental and stellate ganglion blocks, may produce adverse reactions similar to systemic toxicity seen with unintentional intravascular injection of larger doses.
10. Bupivacaine should be used with caution in patients with known agent sensitivities. Patients allergic to ester derivatives of para-aminobenzoic acid (procaine, tetracaine, benzocaine etc.) have not shown cross sensitivity to agents of the amide type.
11. Bupivacaine should be used with caution in patients with a genetic predisposition to malignant hyperthermia as the safety of amide local anaesthetic agents in these patients has not been fully established. A standard protocol for the management of malignant hyperthermia should be available.
12. Adrenaline-containing solutions should be used with extreme caution in patients with severe or untreated hypertension, arteriosclerotic heart disease, cerebral vascular insufficiency, heart block, or any other pathological condition that might be aggravated by the effects of adrenaline. Adrenaline may induce anginal pain in patients suffering from angina pectoris.
13. Solutions containing adrenaline should be used with caution in patients with ventricular fibrillation, prefibrillatory rhythm, tachycardia, myocardial infarction, phenothiazine induced circulatory collapse and prostatic hypertrophy. (See CONTRAINDICATIONS, ADVERSE EFFECTS and INTERACTIONS).

Use during pregnancy

The safe use of bupivacaine during pregnancy has not been established. Although bupivacaine has been used extensively for dental procedures during pregnancy with no reports of ill effects to mother or foetus, there are no adequate well controlled studies in pregnant women of the effect of bupivacaine on the developing foetus. It should therefore be used cautiously during pregnancy.

Adrenaline has been given to large numbers of pregnant women and women of child-bearing age without any proven increase in the frequency of malformation or other indirect harmful effects on the foetus having been observed.

Adrenaline may delay the second stage of labour by inhibiting uterine contractions.

Use during lactation

Bupivacaine enters breast milk but in such small quantities at therapeutic dose levels that there is generally little risk of affecting the child.

Effects on ability to drive and use machines

Depending on the dosage, local anaesthetics may have a mild effect on mental function and co-ordination and may temporarily impair locomotion and co-ordination.

Adverse Effects

Reactions to bupivacaine are similar in character to those observed with other local anaesthetics of the amide type.

These adverse reactions are, in general, dose-related and may be due to high plasma levels as a result of excessive dosage, rapid absorption, delayed elimination or metabolism, or inadvertent intravascular injection. Pronounced acidosis, hyperkalaemia or hypoxia in the patient may increase the risk and severity of toxic reactions.

Such reactions are systemic in nature and involve the central nervous system and/or the cardiovascular system (see OVERDOSAGE).

Ventricular arrhythmia, ventricular fibrillation, sudden cardiovascular collapse and death have been reported when 0.5% Marcain[®] DENTAL with Adrenaline 1:200,000 has been utilised for local anaesthetic procedures that may result in high systemic concentrations of bupivacaine.

The following are the most commonly reported adverse effects irrespective of the route of administration.

Central Nervous System

CNS manifestations are excitatory and/or depressant and may be characterised by light-headedness, nervousness, apprehension, euphoria, confusion, dizziness, drowsiness, tinnitus, blurred vision, vomiting, sensations of heat, cold or numbness, twitching, tremor, convulsions, unconsciousness, respiratory depression and/or arrest, agitation, difficulty swallowing and slurred speech.

The excitatory manifestations may be very brief or may not occur at all, in which case the first manifestation of toxicity may be drowsiness merging into unconsciousness and respiratory arrest. Drowsiness following administration of bupivacaine is usually an early sign of a high blood level of the agent and may occur as a result of rapid absorption. In unconscious

patients, circulatory collapse should be watched as CNS effects may not be apparent as an early manifestation of toxicity and may in some cases progress to frank convulsions and ultimately lead to respiratory depression and/or arrest. It is crucial to have resuscitative equipment and anticonvulsant medicines available to manage such patients (see OVERDOSAGE - Treatment of overdose).

Cardiovascular

Cardiovascular manifestations are usually depressant and are characterised by bradycardia, hypotension, and cardiovascular collapse, which may lead to cardiac arrest. (See Overdosage).

Allergy

Allergy to amide type local anaesthetics is very rare but may present as cutaneous lesions, urticaria, odema or anaphylaxis. Patients allergic to ester derivatives of para-aminobenzoic acid (procaine, tetracaine, benzocaine etc.) have not shown cross sensitivity to agents of the amide type.

Sodium metabisulphite is included in solutions containing adrenaline and may also cause this type of reaction.

Neurological Reactions:

The incidence of adverse neurological reactions associated with the use of local anaesthetics is very low.

Interactions

Anti-arrhythmic medicines

Local anaesthetics of the amide type, such as bupivacaine should be used with caution in patients receiving anti-arrhythmic medicines (e.g. Mexiletine) since potentiation of cardiac effects may occur.

The following interactions may occur with adrenaline-containing solutions:-

CNS acting agents

Solutions containing adrenaline should be used with extreme caution in patients receiving tricyclic antidepressants, phenothiazines, monoamine oxidase inhibitors, butyrophenones or some antihistamines and thyroid hormones as severe sustained hypertension or hypotension and/or potentiation of adrenaline-induced cardiovascular effects may result.

Oxytocic agents of the ergot-type

Adrenaline-containing solutions should not be used in the presence of oxytocic agents of the ergot-type as they are known to interact to produce severe, persistent hypertension and its sequelae.

Adrenergic neuron blocking agents

Solutions containing adrenaline should be used with caution in the presence of adrenergic neuron blocking agents (e.g. guanethidine, debrisoquine, bethanidine).

Inhalation anaesthetics

Serious cardiac arrhythmias and acute pulmonary oedema if hypoxia is present may occur if preparations containing adrenaline are employed in patients during or following the administration of chloroform, halothane, cyclopropane, trichlorethylene, or other halogenated compounds.

Cardiac glycosides

Solutions containing adrenaline may enhance the toxic effects of cardiac glycosides which may result in arrhythmias.

Quinidine

Solutions containing adrenaline may interact with quinidine resulting in cardiac arrhythmias.

Hypoglycaemic agents

Adrenaline induced hyperglycaemia may lead to loss of blood sugar control in diabetic patients treated with hypoglycaemic agents.

Overdosage

Acute emergencies associated with the use of local anaesthetics are generally related to high plasma levels or to unintended subarachnoid injection of the local anesthetic solution (See ADVERSE EFFECTS and WARNINGS AND PRECAUTIONS).

With accidental intravascular injections of local anaesthetics, the toxic effects will be obvious within 1-3 minutes. With overdosage, peak plasma concentration may not be reached for 20-30 minutes, depending on the site of injection and toxic signs will be delayed. Toxic reactions mainly involve the central nervous and cardiovascular systems.

Acute systemic toxicity

Central nervous system toxicity is a graded response with symptoms and signs of escalating severity. The first symptoms are circumoral paraesthesia, numbness of the tongue, light-headedness, hyperacusis and tinnitus. Visual disturbance and muscular tremors are more serious and precede the onset of generalised convulsions. These signs must not be mistaken for neurotic behaviour. Unconsciousness and grand mal convulsions may follow which may last from a few seconds to several minutes. Hypoxia and hypercapnia occur rapidly following convulsions due to the increased muscular activity, together with the interference with normal respiration and loss of the airway. In severe cases, apnoea may occur.

Cardiovascular toxicity indicates a more severe situation. Hypotension, bradycardia, arrhythmia and even cardiac arrest may occur as a result of high systemic concentrations of local anaesthetics. Cardiovascular toxic effects are generally preceded by signs of toxicity in the central nervous system, unless the patient is receiving a general anaesthetic or is heavily sedated with drugs such as benzodiazepines or barbiturates.

Treatment of overdosage

If signs of acute systemic toxicity appear, injection of the local anaesthetic should be stopped immediately.

Treatment will be required if convulsions occur. All medicines and equipment should be immediately available. The objectives of treatment are to maintain oxygenation, stop the convulsions and support the circulation. Oxygen must be given and ventilation assisted if necessary (mask and bag). An anticonvulsant should be given IV if the convulsions do not stop spontaneously in 15-20 seconds, Thiopentone 100-150 mg IV will abort the convulsions rapidly.

Alternatively diazepam 5-10 mg IV may be used, although its action is slower. Suxamethonium will stop the muscle convulsions rapidly, but will require tracheal intubation and controlled ventilation, and should only be used by those familiar with these procedures.

Pharmaceutical Precautions

Shelf-life

18 months

Storage

Stored at or below 25°C. Do not freeze. Protect from light.

Local anaesthetics react with certain metals and cause the release of their respective ions which, if injected, may cause severe local irritation. Adequate precautions should be taken to avoid prolonged contact between 0.5% Marcain[®] DENTAL with Adrenaline 1:200,000 solutions and metal surfaces such as metal bowls, cannulae and syringes with metal parts.

Adrenaline-containing solutions should not be re-autoclaved. Surface sterilisation using pure, undiluted isopropyl alcohol (91%) or 70% ethyl alcohol (USP) may be carried out if desired.

Medicine Classification

Prescription Medicine

Package Quantities

0.5% Marcain[®] DENTAL with Adrenaline 1:200,000, 50 x 2.2 mL.

Further Information

Excipients

- Sodium chloride
- Sodium metabisulphite
- Hydrochloric acid
- Sodium hydroxide
- Water for injections

Name and Address

Sponsor:
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