SCHEDULING STATUS: S4

PROPRIETARY NAME (AND DOSAGE FORM):

HYALASE (Powder for Injection)

COMPOSITION:

Hyalase is a purified and standard preparation of the enzyme hyaluronidase in the form of a sterile, freeze-dried powder. Each ampoule contains 1 500 international units of hyaluronidase.

Sugar free.

PHARMACOLOGICAL CLASSIFICATION:

A 31 Enzymatic preparations

PHARMACOLOGICAL ACTION:

Hyaluronidase has a temporary and reversible depolymerizing action on the polysaccharide hyaluronic acid which is present in the intercellular matrix of connective tissue. This intercellular "cement" is thereby made more permeable, permitting the rapid dispersal and absorption of injected substances, the reduction of tissue tension and the dispersal of extravascular fluid in joint and tissue damage.

INDICATIONS AND DOSAGE AND DIRECTIONS FOR USE:

1. **Hypodermoclysis**

   An ordinary two way subcutaneous infusion set is required with the fluid container supported about 1 meter above the patient. Suitable hypodermic needles (Record No. 12) are attracted to the connecting tubes after any contained air has been expelled. The needles are then inserted into the subcutaneous tissues at selected sites and the fluid allowed to run in by gravity. The contents of one

ampoule of Hyalase (1 500 international units), dissolved in one millilitre of sterile distilled water, are injected through the tubing about 2,5 cm from each needle. When this method is employed, approximately 200 ml of fluid can be administered in 20 minutes.

The rate of administration can be further varied by raising or lowering the reservoir, but whenever greater speed is required, with possibly smaller volumes, the rate may be increased by injecting the fluid from a 20 ml or 50 ml syringe, the appropriate amount of solution of Hyalase being drawn into the syringe beforehand.

Repeated infusions may be given as required, but it is advisable to change the site of injection. As solutions of the enzyme lose their activity in 12 – 24 hours, it is important that fresh solutions are prepared prior to each administration.

Injection may alternatively be given from a syringe directly into a site into which 1 ml of sterile distilled water containing 1 500 international units of Hyalase has previously been injected. The needle should be maintained in the site adopted throughout the procedure which, in this case, should not be unduly prolonged. It is not advisable to raise the temperature of the fluid prior to infusion since this has been observed to reduce the rate of absorption.

Site of Injection

One of the great advantages of hypodermoclysis is that the possible sites of administration are numerous, irrespective of the position of the patient. Choice may be made for example, from the axilae, pectoral regions, subscapular and trunk areas, thighs and calves. The intramedullary route has also been used successfully (e.g. sternum and tibia). In children, Gaisford and Evans consider the anterior abdominal wall presents the best site from the point of view of maximal absorption and freedom from napkin contamination. In this case one needle is inserted on each side of, and about 2,5 cm from the umbilicus and directed laterally. In general 1 500 international units of Hyalase are sufficient for

the administration of 500 – 1 000 ml of most fluids. In the case of whole blood, however, 3 000 units may be required.

2. **Obstetric anaesthesia**

The anaesthetic moisture is prepared as follows:

Hyalase – 1 500 international units

Adrenaline hydrochloride – 0,5 ml of 1: 1 000 dilution

Procaine hydrochloride– 30 ml of 1 % solution.

Hein's method is as follows:

"The needle is passed horizontally to the ischial spine, and 5 ml of the solution is deposited here to anaesthetise the pudendal nerve as it enters Alcock's canal. Next, 5 ml of the mixture is infiltrated in the superior portion of the labia minora to anaesthetise the perineal branches of the ilioinguinal nerve. The same procedure is carried out on both sides of the perineum."

3. Prevention of post-partum haemorrhage

When ergometrine is given intramuscularly together with Hyalase, at the crowning of the foetal head, the oxytocic effect of the drug is apparent 3 – 4 minutes earlier than when ergometrine is given alone and approximates to the effect seen after intravenous ergometrine.

This technique is particularly useful when the doctor or midwife is working alone and the intravenous administration of ergometrine is impractical. Extensive trials have shown that the routine use of intramuscular ergometrine /Hyalase shortens the third stage of labour without increasing the danger of retained placenta, and produces striking reduction in the incidence of post partum haemorrhage. The injection solution is made by dissolving the contents of one ampoule of Hyalase 1 500 I.U in 1 ml of ergometrine solution containing 0,5 mg of ergometrine. This solution is prepared a little before it is needed and is held ready in the syringe; at the moment of the crowning of delivery of the foetal head it is injected intramuscularly into the thigh.

CORRECT TIMING IS MOST IMPORTANT.

4, **As an aid to local anaesthesia in ophthalmology**

The solution employed consists of a 2 % solution of procaine hydrochloride and 0,4 % potassium sulphate. One drop of adrenaline hydrochloride (1:1 000) and approximately 150 international units of Hyalase are added to each 5 ml of the solution. Two further drops of adrenaline are added for cone injections if this is not contra-indicated.

150 units are obtained by injecting 1,0 ml of distilled water, or other fluid into an ampoule of Hyalase and withdrawing 0,1 ml. In order to provide a more concentrated solution of adrenaline for injections of the muscle cone and to avoid using more than three drops of adrenaline, the following procedure may be adopted:

Six millilitres of anaesthetic solution are drawn into a syringe, one drop of adrenaline is then added. An injection of 3 ml is then made into the temporofacial nerve at the site recommended byO'Brien. Following this procedure, two additional drops of adrenaline may be added to the remainder of the solution in the syringe prior to injection of the cone.

5. As an aid to local anaesthesia in fracture reduction

The method described by Thorpe is as follows:

"Before injection, the local anaesthetic agent (for Colles' fracture 20 ml of 1 % procaine) is mixed with 1 500 international units of Hyalase.

Two injections are made: the bulk of the solution is put directly into the fracture haematoma from the extensor aspect of the forearm, and 2-3 ml are infiltrated around the ulnar styloid process.

The anaesthetic solution disperses rapidly all around the injured area and the fracture can be manipulated as soon as the needle is withdrawn."

For Pott's fracture, Thorpe recommends 40 ml of 1 % procaine and 1 500 international units of Hyalase.

6. Radiography

The following method for the subcutaneous administration of radio-opaque substances with hyaluronidase in pyelography is now generally adopted.

(a) The contents of one ampoule of Hyalase are dissolved in 1,0 ml of sterile distilled water. (A fresh solution must be prepared on each occasion).

(b) 0,5 ml of Hyalase solution is then added to 5 ml of 35 % diodone solution and made up to15 ml with sterile distilled water (this operation may be carried out in a 20 ml syringe).

(c) Fifteen millilitres of the mixture are injected subcutaneously in the scapular region and are followed immediately by a further 15 ml at another site e.g. the contra-lateral scapular region.

(d) The area of injection is massaged vigorously to aid dispersion. Normally, renal secretion commences five minutes after injection; adequate concentration is obtained in 25 minutes and is equal to that obtained by the intravenous method.

Children

The volumes stated are also applicable to children aged from a few weeks to five years, provided that renal function is not grossly impaired.

CONTRA-INDICATIONS:

Not to be used to reduce the swelling of bites or stings or at sites where infection or malignancy is present. Not to be used for intravenous injection.

SIDE-EFFECTS AND SPECIAL PRECAUTIONS:

For all practical purposes Hyalase is a non-toxic preparation. Doses of up to 2 000 mg/kg have been given to mice without any evidence of toxicity. However, sensitivity

to hyaluronidase occasionally occurs. The administration of salicylates inhibits the spreading action of hyaluronidase. Hyaluronidase may be added to the injection fluid or may be injected into the site before the fluid is administered.

However, dextrose should always be administered as a hypo-osmotic solution, and if there is dehydration, electrolytes should only be given to infants and children on hypo-osmotic solution. Care should be taken in the treatment of children to control the speed and total volume administered to avoid overhydration.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

None on record.

IDENTIFICATION:

Ampoules containing a dry, white, fluffy powder.

PRESENTATION:

Ampoules each containing 1 500 international units of hyaluronidase packed in boxes of 10 ampoules.

STORAGE INSTRUCTIONS:

Store below 25 ºC. Use immediately after preparation.

No need to refrigerate.

KEEP OUT OF REACH OF CHILDREN.

REFERENCE NUMBER:

H 2874 (Act 101/1965)

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION:

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