Wed 19 Sept 0740-0800 Dr Phillip Artemi Pharmacology of Phlebology

PHARMACOLOGY OF PHLEBOLOGY

Phillip Artemi

MECHANISM OF ACTION OF SCLEROTHERAPY

GENERAL MECHANISM FOR PRODUCING ENDOTHELIAL DAMAGE

Sclerotherapy refers to the introduction of a foreign substance into the lumen of a vessel causing thrombosis and subsequent fibrosis. This procedure, when performed on telangiectasia, is referred to as microsclerotherapy.

The mechanism of action for sclerosing solutions is that of producing endothelial damage (endosclerosis) that causes endofibrosis. The extent of damage to the blood vessel wall determines the effectiveness of the solution.

Total endothelial destruction results in the exposure of sub-endothelial collagen fibers causing platelet aggregation, adherence, and release of platelet-related factors. This series of events initiates the intrinsic pathway of blood coagulation by activating factor XII. Ideally, sclerosing solutions otherwise should not cause activation or release of thromboplastic activity because this would initiate the extrinsic pathway of blood coagulation.

Excessive thrombosis is detrimental to the production of endofibrosis because it may lead to recanalization of the vessels as well as excessive intravascular and perivascular inflammation and its resulting sequelae. This can be prevented or at least minimized with post-sclerotherapy compression. However, thrombosis usually occurs to some degree as a result of sclerotherapy. If a thrombus is formed, it should be well anchored to the venous wall to prevent embolization. Wolf in 1920 established that effective sclerosis causes thrombosis that penetrated the full thickness of the adventitia of the vessel wall. Schneider has shown in histologic examinations of scierosed varices that the strongest fixation of a thrombus occurs in areas where the entire endothelium is destroyed. Therefore endothelial damage must be complete and should result in minimal thrombus formation with subsequent organization and fibrosis. In addition, after sclerotherapy, maximum full-thickness fibrosis of the treated segment occurs after 6 weeks of compression. Therefore, in addition to limiting the extent of thrombosis, compression may facilitate endofibrosis.

For sclerotherapy to be effective without recanalization of the thrombotic vessel, the endothelial damage and resulting vascular necrosis must be extensive enough to destroy the entire *blood* vessel wall.

Destruction of the entire vessel wall and not just the endothelium is necessary. The reason may relate to the multifunctional nature of vascular smooth muscle cells. These cells, which are found in significant concentration within superficial veins, have a large number of functions including the synthesis of collagen, elastin, and proteoglycans. It is hypothesized that if they remain viable, they can regenerate a foundation that promotes migration of undamaged adjacent endothelial cells that allow recanalization of the treated vessel.

In addition, for effective destruction of a varicosity or telangiectasia, the entire vessel must be sclerosed to prevent recanalization. Recanalization occurs easily in vessels where only a section of endothelium is damaged. This is due to rapid

endothelial regeneration, which has been measured at a turnover rate of *0.1%* to *10%* per day or higher.

CATEGORIES OF SCLEROSING SOLUTIONS

All sclerosing solutions can be placed into three broad categories based on their mechanisms for producing endothelial injury: detergent, osmotic, or chemical.

Detergent Solutions

Detergent sclerosing solutions commonly used to treat varicose and telangiectatic veins include sodium morrhuate (SM), ethanolamine oleate (EO), sodium tetradecyl sulfate (STS), and polidocanol (POL). They produce endothelial damage through interference with cell surface lipids. Strong detergents, such as STS and SM, produce maceration of the endothelium within I second of exposure. The intercellular “cement” is disrupted, causing desquamation of endothelial cells in plaques. Because the hydrophilic and hydrophobic poles of the detergent molecule orient themselves so that the polar hydrophilic part is within the water and the hydrophobic part is away from the water, they appear as aggregates in solution (micelles) or fixed onto the endothelial surface. Strong detergent sclerosants therefore have a low safety margin.

Detergents act as micelles when injected into a non-detergent environment (blood). Their destructive action on endothelial cells is enhanced when they act as aggregates rather than monomers. Thus the concentration of the sclerosing solution in the vessel is an important factor regarding endothelial destruction and activity. They have been found to aggregate to a significant extent at higher temperatures versus room temperatures.

Effective endosclerosis occurs through damage to endothelium and not through thrombosis induced by destruction or damage to red and/or white blood cells.

Osmotic Solutions

Hypertonic solutions such as hypertonic saline (HS) probably cause dehydration of endothelial cells through osmosis causing endothelial destruction, It is speculated that fibrin deposition with thrombus formation on the damaged vessel wall occurs through modification of the electrostatic charge of the endothelial cells. For the vessel wall to be completely destroyed, the osmotic solution must be of sufficient concentration to diffuse throughout the entire vein wall. In contrast to the immediate action of detergent sclerosing solutions, experimental studies have shown that endothelial destruction with HS 22% or glucose 66% occurs only after 3 minutes. The destroyed endothelial cells do not appear to be desquamated as with detergent sclerosing solutions.

Hypertonic *solutions* have a predictable destructive power that is proportional to their osmotic concentration. Ranked the
solutions from strongest to weakest as the following:

1. Sodium salicylate 40%
2. Sodium chloride 10% + sodium salicylate 30%
3. Invert sugar 75%
4. Saccharose 5%
5. Phenoll%
6. Dextrose 66%
7. Sodium chloride 20%
8. Sodium salicylate 30%

The authors concluded that maximal endothelial destruction occurred as early as

30 minutes to 4 days after injection, after which time the injected vessel went through either a reparative or a fibrotic process.

Because dilution occurs with intravascular serum and blood osmotic solutions, have their greatest effect at or near the site of injection. In contrast, detergent-scleroslng solutions can exert effective sclerosis for 5 to 10 cm along the course of the injected vessel. HS 23.4% is more potent (about two to three times more) than POL 0.5%. Detergent solutions have about twice the therapeutic efficacy of osmotic solutions. A better comparison would have been with HS 11.7%.

Chemical Solutions
Chemical irritants also act directly on endothelial cells to produce endosclerosis. 4% polyiodinated ions. The chemical destruction is in part related to the dissolution of intercellular cement, which has been demonstrated to occur after 30 seconds of exposure.

Aethoxyskierol
Composition *Active.* Laureth-9 (polidocanol).
Inactive. Ethanol, dibasic sodium phosphate dehydrate, monobasic potassium phosphate, water for injections. Aethoxysklerol is buffered to pH 6.5 to 8.0.

Pharmacokinetics. Following the IV administration of 14C-laureth-9 solution into the saphenous vein of six healthy male volunteers, blood was collected over 12 hours and urine and faeces collected over 96 hours. After 12 hours 89% of the dose was eliminated from the blood. A total of 48% of the radioactive dose was recovered in urine (21 %) and faeces
(27%).

Contraindications Known allergy to laureth-9 or any of the excipients; Bed-ridden patients and patients unable to walk;

Arterial disease such as severe artherosclerotic peripheral vascular disease; Patients with thromboembolic disorders and patients with high risk of thrombosis (those with multiple risk factors such as taking oral contraceptive tablets, adiposis, smoking, longer periods of immobilization).

Other contraindications include acute superficial thrombophlebitis; significant valvular or deep vein incompetence; huge superficial veins with wide open communications to deeper veins; acute cellulitis; allergic conditions; acute infections; varicosities caused by abdominal and pelvic tumours unless the tumour has been removed; uncontrolled systemic disease such as diabetes, toxic hyperthyroidism, tuberculosis, asthma, neoplasm, sepsis, blood dyscrasias and acute respiratory or skin diseases.

Depending on severity, sclerotherapy may be contraindicated in: leg oedema (if it cannot be influenced by compression); Symptoms of diabetic microangiopathy;

Inflammatory skin reactions in the injection area;

Acute severe cardiac diseases (endocarditis, myocarditis). Note that heart failure, if stabilized by previous treatment, is not a contraindication to sclerotherapy. The same applies to arterial hypertension if it has been adequately managed by previous treatment;

Febrile states;

Advanced age with impaired mobility or very poor general condition.

Carcinogenesis, mutagenesis, impairment of fertility. The carcinogenic potential of laureth-9 has not been adequately assessed in long-term animal studies. In short-term studies investigating the genotoxic potential of laureth-9, no evidence of mutagenecity was noted; however, a concentration dependent increase in the incidence of chromosomal abnormalities (polyploid cells) was observed in cultured Chinese hamster fibroblasts, suggesting a possible genotoxic effect of the drug.

Impairment of fertility. No effect on fertility was observed when male and female rats were treated intermittently with laureth-9 at intravenous doses up to 10 mg/kg (once a week exposure in rats was about 80% of the maximum human dose in terms of surface area prior to mating.

Use in pregnancy. There are no adequate and well controlled studies in pregnant women. Therefore, laureth-9 should not be used in pregnant women.

Use in lactation. It is not known whether laureth-9 is excreted into human milk. Because many drugs are excreted in human milk, caution should be exercised when Aethoxysklerol is administered to a breastfeeding woman.

Use in children. There are no data and therefore Aethoxysklerol is not recommended for use in children.

Interactions There are no data on drug interactions with laureth-9.

Adverse Reactions Pivotal clinical trial. Aethoxysklerol and sodium tetradecyl sulfate injection caused reactions that were expected based upon the known pharmacological properties of the drugs and/or the mode of application of the drug (needle injection). Immediate local reactions (pain on injection, inflammation swelling and local allergic reactions) and delayed local reactions (hyperpigmentation, vein thrombosis, ecchymoses and neovascularisation) were all related to the injected agent and to the known effects on vascular endothelium. In both groups the most common repeated adverse events were hyperpigmentation, vein thrombosis, ecchymoses and pain on injection. (See Table)

Aethoxysklerol

AII adverse events (independent of the number of treatments per patienf)

.	**OHIO substudy**		**MICA substudy**	
	STS	**Aethoxvsklerol**	STS	**Aethoxvsklerol**
n	75	75	91	81
Any	89%	88%	100%	98%
Hvperpigmentation	72%	65%	64%	53%
Skin necrosis	4.0%	2.7%	5.5%	0.0%
Rash		-	**8.8%**	**11%**
	OHIO substudy		**MICA Substudy**	
	STS	**Aethoxvsklerol**	**STS**	**Aethoxvsklerol**
Vein thrombosis*	59%	61%	46%	42%
Neovascularisation	5.3%	9.3%	11%	7.2%
Ecchymosis	63%	49%	70%	58%

Pain	31%	45%	41%	43%
Local allerav	4.0%	6.7%	36%	23%
Inflammation	4.0%	0.0%	59%	41%
Swelling Oedema	-		40% 2.2%	19% 0.0%
Taste disturbance	0.0%	2.7%	1.1%	0.0%
Visual field defect	-	.	1.1%	0.0%
Paraesthesia	0.0%	1.3%	2.2%	3.6%
Dizziness		-	2.2%	0.0%

* It should be noted that while vein thrombosis is reported as an adverse event, it is often part of the pharmacological mechanism of action of laureth-9 and is expected with sclerotherapy. STS = sodium tetradecyl sulfate

Postmarketing. Spontaneous reporting worldwide of adverse events associated with the use of Aethoxysklerol are as follows.

Uncommon (> 1,1000, < 1/100). Skin. Pigmentation at injection site: discolouration (hyperpigmentation, less frequently haematomas) and neovascularisation in the sclerosed area.

Vascular. Pain or phlebitis along the injected vein. Vascular. Thrombosis formation, locally at the injected vein. *Rare (> 1/10,000, < 1/1,000).* Skin/vascular. Superficial venous inflammation (periphlebitis. thrombophlebitis) and local tissue death (necrosis), particularly after inadvertent injection into adjacent tissue (perivascular injection); the risk increases in proportion to the Aethoxysklerol concentration.

Skin/body as a whole. Allergic/sensitivity reactions: local allergic and non-allergic skin reactions, very rarely systemic allergic reactions such as anaphylactic shock, angioedema or asthmatiform reactions.
Very rare ((1/10,000). Vascular. Deep vein thrombosis of unknown aetiology, that may have been due to the underlying disease.

Cardiovascular. Cardiovascular problems (collapse, dizziness). Cardiovascular. Breathing difficulties and sensation of pressure in the chest. Gastrointestinal. Nausea.
Visual. Visual disturbances.

Special senses. Locally impaired sensitivity and taste sensations (metallic or furry taste). Body as a whole. Fever and headache.

Dosage and Administration Dosage and selection of the Aethoxysklerol concentration depends on the size of the varices to be sclerosed. The maximum dosage 2 mg/kg bodyweight per day must not be exceeded. Two weeks may be necessary, depending on the severity and extent of the varices and on the success of the previous treatments.

Overdosage Overdose (caused by injection of an excessive amount of Aethoxysklerol for the vein size being injected) may result in local necrosis, especially if extravasation occurred. No serious sequelae were observed in patients who received Aethoxyskierol doses in excess of the recommended maximum dose of 2 mg/kg bodyweight per day.

Fibro-Vein

Composition *Active.* Sodium tetradecyl sulfate *Inactive.* Benzyl alcohol 2%; buffered to pH 7.6.
Actions The action of sodium tetradecyl sulfate in compression sclerotherapy is considered to be that of irritation to the intima of the vein wall, so that on compression of the vein, fibrosis takes place and the vein is permanently occluded by the development of fibrosis in the wall and across the lumen of the compressed vein.

Contraindications Allergy to sodium tetradecyl sulfate or to any component of the preparation.

Patients unable to walk due to any cause.

Patients currently taking oral contraceptives. Significant obesity.

Acute superficial thrombophlebitis. Local or systemic infection. Varicosities caused by pelvic or abdominal tumours. Uncontrolled systemic disease, e.g. diabetes mellitus. Significant valvular incompetence requiring surgical treatment.
Precautions

Allergy and anaphylaxis
A higher incidence of allergic reaction is thought to result from repeated treatment involving sodium tetradecyl sulfate injection and may involve intervals of several years between courses of injection. Where special caution is indicated a test dose of 0.25 to 0.5 mL. FibroVein should be given up to 24 hours before any further therapy.

Special care should be exercised when injecting above and posterior to the medial malleolus where extravascular injection is in danger of being close to the posterior and tibial artery. Pigmentation can result if blood is extravasated at the injection site, particularly when treating the smaller surface veins, and compression is not used.

Extreme caution in use is required in patients with an arterial disease such as severe peripheral atherosclerosis of thromboangiitis obliterans (Buerger's disease).

Use in pregnancy. Safety for use in pregnancy has not been established. Use only when clearly needed for symptomatic relief and when the potential benefits outweigh the potential hazards to the foetus.

Use in lactation. It is not known whether sodium tetradecyl sulfate is distributed into human milk. Caution should be exercised when used in breastfeeding mothers.

Adverse Reactions *Local.* Pain or burning. Skin pigmentation. Tissue necrosis and ulceration may occur with extravasation. Paraesthesia and anaesthesia may occur if an injection affects a cutaneous nerve.

Vascular. Superficial thrombophlebitis. Deep vein thrombosis and pulmonary embolism are very rare. Inadvertent intraarterial injection is very rare, but may lead to gangrene. Most cases have involved the posterior tibial artery above the medial malleolus.

Systemic reactions. Allergic reactions are rare, presenting as local or generalized rash, urticaria, nausea or vomiting, asthma, vascular collapse. Anaphylactic shock, which may potentially be fatal, is extremely rare.

ANTICOAGGULANTS

Clexane

Composition *Active.* Enoxaparin sodium, *Inactive.* Water for injections.
Actions. In comparison with natural heparin, Clexane is characterized by a clear increase in the ratio between anti-Xa and anti-ha activities, which is always greater than four.

It has several actions on the coagulation pathway through binding to antithrombin Ill. The antithrombotic activity is related to inhibition of thrombin generation and inhibition of two main coagulation factors: factor Xa and thrombin.

Pharmacokinetics. The pharmacokinetic parameters of Clexane were studied from the changes in plasma anti-Xa activity.

After injection of Clexane by the subcutaneous route, the product is rapidly and completely absorbed. The absolute bioavailability is over 90%.

The maximum plasma activity is observed after three hours and is, on average, 1.6 microgram/mL after the injection of a 40 mg dose.

The elimination of enoxaparin (based on anti-Xa activity levels) is characterized by a half-life of approximately 4.4 hours for a dose of 40 mg. Following a 40 mg dose, anti-Xa activity may persist in the plasma for 24 hours.

Elimination of Clexane at prophylactic dosages is not significantly modified in patients with mild (creatinine clearance 50 to 80 mL/minute) to moderate (creatinine clearance 30 to 50 mL/minute) renal insufficiency. It is slightly reduced in the elderly (t1/2 = six to seven hours). This modification has no effect on the doses or the frequency of injection, as there is no plasma accumulation in elderly subjects. The anti-Xa activity generated by Clexane does not cross the placental barrier during the second trimester of pregnancy.

Anti-Xa activity is generated by Clexane is focalized within the vascular space. Metabolic breakdown of Clexane is slight and takes place mainly in the liver (desulfation and depolymerisation). Small amounts of the product are eliminated by the kidneys in an intact or slightly degraded form.

Renal impairment. A linear relationship between anti-Xa plasma clearance and creatinine clearance at steady state has been observed, which indicates decreased clearance of Clexane in patients with reduced renal function

Weight. There is a lower weight adjusted clearance (L1hour/kg) in obese subjects Elderly. Based on the results of a pharmacokinetic analysis. the Clexane kinetic profile is not different in elderly subjects compared to younger subjects when renal function is normal. However, since renal function is known to decline with age, elderly patients may show reduced elimination of Clexane.

Indications Prevention of thromboembolic disorders of venous origin in patients undergoing orthopaedic and general surgery.

Prophylaxis of venous thromboembolism in medical patients bedridden due to acute illness. Prevention of thrombosis in extracorporeal circulation during

haemodialysis.

Treatment of established deep vein thrombosis.

Treatment of unstable angina and non-Q-wave myocardinal infarction, administered concurrently with aspirin.

Contraindications Allergy to Clexane, heparin or its derivatives including other low molecular weight heparins. Acute bacterial endocarditis.

Conditions with a high risk of uncontrolled haemorrhage including major bleeding disorders, focal lesions, haemorrhagic stroke, active ulcerative conditions showing a tendency to haemorrhage (e.g. peptic ulcer, ulcerative colitis).

Precautions
Clexane is to be used with extreme care in patients with a history of heparin induced (including low molecular weight heparins) thrombocytopenia with or without thrombosis. The risk of heparin induced thrombocytopenia may persist for several years. If history of heparin induced thrombocytopenia is suspected, in vitro platelet aggregation tests have limited predictive value. The decision to use Clexane in such a case must be made only in consultation with an expert in the field.

Not to be administered by the intramuscular route.

Clexane should be used with care in patients with the following conditions: hepatic insufficiency, uncontrolled arterial hypertension, a history of gastrointestinal ulceration, impaired haemostasis, recent ischaemic stroke, diabetic retinopathy, recent neurological or ophthalmological surgery.
Pharmacokinetics of enoxaparin are altered in renal impairment.

Haemorrhage. As with other anticoagulants, bleeding may occur at any site.

Monitoring of platelet count. The risk of antibody mediated heparin induced thrombocytopenia also exists with low molecular weight heparins. Should thrombocytopenia occur, it usually appears between the 5th and the 21st day following the beginning of Clexane treatment. Therefore, it is recommended that the platelet counts be measured before initiation of therapy with Clexane and then regularly thereafter during the treatment. In practice, if a confirmed significant decrease of the platelet count is observed (30 to 50% of the initial value), Clexane treatment must be immediately discontinued and the patient switched to another therapy.

Low weight. An increase in exposure of Clexane with prophylactic dosages (non-weight adjusted) has been observed in low weight women (<45 kg) and low weight men (<57 kg), which may lead to a higher risk of bleeding. Therefore, careful clinical monitoring is advised in these patients.

Impaired renal function. In patients with renal impairment, there is an increase in exposure of Clexane which increases the risk of bleeding. Since exposure of Clexane is significantly increased in patients with severe renal impairment (creatinine clearance <30 mL/minute), a dosage adjustment is recommended for therapeutic and prophylactic dosage ranges. Although no dosage adjustment is recommended in patients with moderate (creatinine clearance 30 to 50 mLfminute) and mild (creatinine clearance 50 to 80 mL/minute) renal impairment, careful

clinical monitoring is advised (see Dosage and Administration). Pharmacokinetics of enoxaparin are altered in renal impairment. The extent to which a defect in platelet function in severe renal failure might further contribute to bleeding risk is unknown.

Use in the elderly. No increased bleeding tendency is observed in the elderly with the prophylactic dosage ranges. Elderly patients (especially 80 years or older) may be at an increased risk for bleeding complications with the therapeutic dosage ranges. Careful clinical observation is advised. A dosage adjustment may be necessary in elderly patients due to age related impairment of renal function (see Dosage and Administration, Renal impairment).

Use in pregnancy. (Category C) Animal toxicity studies have shown that Clexane may have some effect on rat and rabbit reproduction. There is no information available concerning the use of Clexane during the first and third trimesters. As there are no adequate and well controlled studies in pregnant women and because animal studies are not always predictive of human response, this drug should be used during pregnancy only if the doctor has established a clear need.

Use in lactation. Studies performed in female rats demonstrated that Clexane has no effect on lactation or milk composition. Effects of Clexane on breastfeeding women have not been studied.

As a precaution, women should be advised not to breast feed while using Clexane.

Interactions. Clinical trials revealed no adverse effects that could be caused by drug interactions.
It is recommended that agents which affect haemostasis should be discontinued prior to Clexane therapy unless strictly indicated. These agents include medications such as anticoagulants, thrombolytics, nonsteroidal anti-inflammatory drugs (NSAIDs) (including ketorolac), preparations containing aspirin (acetylsalicylic acid), systemic salicylates, ticlopldlne, dextran 40, clopidogrel, other antiplatelet agents including glycoprotein Iib/ilia antagonists or systemic glucocorticoids. If the combination is indicated, Clexane should be used with careful clinical and laboratory monitoring of the haemostatic factors where appropriate.

Adverse Reactions clinical trial data. The following information relates to adverse events observed in controlled clinical trials with patients given Clexane prophylactically or for the treatment of deep vein thrombosis (n = 1,170) or with patients given Clexane for the treatment of unstable angina or non-Q-wave myocardial infarction, administered concurrently with aspirin (n = *1,578).*

Reported adverse *events* are presented at the following frequencies. Common: *2>:1/100 (1%)* and < 1/10 (10%); uncommon: *2>:1/1,000* (0.1%) and < 1/100 (1%); rare: *2>:1/10,000 (0.01%)* and < *1/1,000* (0.1%); very rare: < *1/10,000 (0.01%).*

Haematologidal. *Common.* Haemorrhage. Bleeding may occur in the presence of associated risk factors such as organic lesions liable to bleed, invasive procedures or the use of medications affecting haemostasis (see Precautions and Interactions). Major haemorrhage including retroperitoneal and intracranial bleeding has been reported. Some of these cases have been fatal.

Blood disorders. *Uncommon.* Thrombocytopenia. Mild, transient, asymptomatic thrombocytopenia has been reported during the first days of therapy.

Hepatic. *Uncommon.* Asymptomatic and reversible increases in the levels of liver enzymes (e.g. transaminases) have been reported.

Postmarketing data. The following information related to events observed following the marketing of Clexane. Voluntary reports of adverse events that have been received since market introduction (without causal relationship) that are not listed previously are cited below.

Haematological. *Very rare.* There have been rare reports of neuraxial haematomas with the concurrent use of Clexane and spinal/epidural anaesthesia and postoperative indwelling catheters. These events have resulted in varying degrees of neurological injuries including long-term or permanent paralysis (see Precautions).

Rare cases of immunoallergic thrombocytopenia with or without thrombosis have been reported. In some cases, thrombosis was complicated by organ infarction or limb ischaemia. Asymptomatic and reversible increases in platelet count levels have been reported.

Hypersensitivity and skin. Injection site. *Veiy rare.* Pain, haematoma and mild local irritation may follow the subcutaneous injection of Clexane.

Hard inflammatory nodules, which are not cystic enclosures of Clexane, have been observed at the injection site. They resolve after a few days and should not cause treatment discontinuation.

Cases of skin necrosis at the injection site have been reported with both unfractionated and low molecular weight heparins. These phenomena are usually preceded by purpura or erythematous plaques, infiltrated and painful. Treatment must be discontinued immediately.

Systemic allergic reactions. *Very rare.* Cutaneous (bullous) or systemic allergic reactions (such as pruritus, rash and urticaria), including anaphylactic/anaphylactoid reactions, may occur. In some cases discontinuation of the treatment may be necessary.

Cases of hypersensitivity cutaneous vasculitis have been reported.

Dosage and Administration Do not mix Clexane with other injections or infusions.

Prophylaxis of venous thrombosis. Prophylaxis against thromboembolism should be tailored according to the patient's risk. Risk factors include age over 40 years, history of deep vein thrombosis or pulmonary embolism, surgery and other trauma, prolonged immobilization, cardiac disease, obesity, malignancy, varicose veins, hyper-coagulable states, pregnancy and post partum, oral contraceptives, severe infection, inflammatory bowel disease.

High risk patients. In patients with high risk of thromboembolism, a dosage of

Moderate risk patients. In patients with a moderate risk of thromboembolism, the recommended dosage is Clexane 20 mg (0.2 mL; 2,000 IU anti-Xa activity) subcutaneously once daily. In moderate risk patients undergoing surgery, the initial dose should be given approximately two hours preoperatively.

Prophylaxis of venous thromboembolism in medial patients. The

recommended dose should be 40 mg once daily by subcutaneous injection for a minimum of six days, continuing for a maximum of 14 days or less if the patient returns to full ambulation earlier than 14 days.

Treatment of deep vein thrombosis. The recommended dosage for treatment of established deep vein thrombosis with Clexane is 1.5 mg/kg bodyweight once daily (150 lU anti-Xa activity/kg bodyweight) or 1 mg/kg bodyweight (100 lU antiXa activity/kg bodyweight) twice daily subcutaneously.

Warfarin sodium therapy should be initiated when appropriate (usually within 72 hours of commencing Clexane initiation). Clexane should be continued for a minimum of five days and until a therapeutic oral anticoagulant effect has been achieved

In the analgesics and anti-rheumatics group, phenylbutazone interacts, however; only a few cases of interactions have been reported with phenilacetic acid derivatives such as fenbufen, indomethacin and sulindac. The arylpropionic acid derivatives ketoprofen and fluriprofen have shown interactions with the coumarins. Piroxicam, isoxicam and paracetamol also interact.

With antimicrobial agents interactions also occur with Rifampicin and erythromycin and there have been isolated reports of interactions with the fluroquinonolones, ciprofloxacin, norfioxacin, ofloxacin, and nalidixic acid. There have been some case reports of interactions with nafcillin, Dicloxacillin, cefamandole, cefazolin, amoxicillin, several Cephalosporins, Griseofulvin, Metronidazole, miconazole, fluconazole, Itraconazole, Ketoconazole, sulfamethoxazoleand cotrimoxazole. There have been reports of a possible interaction with roxithromcyin. No interactions have been seen with temafloxacin and fleroxacin.

Interactions with the following immunosuppressives and anticancer agents have been reported; tamoxifen, Azathioprine, fluorouracil,aminoglutethimide and a combine of ifosfamide and mesna.

The barbiturates Phenobarbital (phenobarbitone) secobarbital (secobarbitone), heptabarbital (heptabarbitone) butabarbital (butabarbitone) and barbital (barbitone) interact with coumarins. No such interaction has been reported for chloral durate.

The antidepressants mianserin, amitriptyline and nortriptyline have been reported not to interact with Warfarin.

Coumadin

Composition. Warfarin sodium.

Actions. Vitamin K dependent factor anticoagulant.
Pharmacology. Coumadin and other coumarin anticoagulants act by inhibiting the synthesis of vitamin K dependent coagulation factors. The resultant in vivo effect is a sequential depression of factors VII, IX, X and II. The degree of depression is dependent upon the dosage administered. Anticoagulants have no direct effect on an established thrombus, nor do they reverse ischaemic tissue damage. However, once a thrombosis has occurred, anticoagulant treatment aims to prevent further extension of the formed clot and prevents secondary thromboembolic complications, which may result in serious and possibly fatal sequelae.

Pharmacokinetics.

Absorption. Coumadin is essentially completely absorbed after oral administration with peak concentration generally attained within the first four hours.

Distribution. There are no differences in the apparent volumes of distribution after intravenous and oral administration of single doses of Warfarin solution.

Metabolism. The elimination of Warfarin is almost entirely by metabolism. Coumadin is selectively metabolised by hepatic microsomal enzymes (cytochrome P450) to inactive hydroxylated metabolites (predominant route) and by reductases to reduced metabolites (Warfarin alcohols). The Warfarin alcohols have minimal anticoagulant activity. The metabolites are principally excreted into the urine and, to a lesser extent, into the bile.

Excretion. The terminal half-life of Warfarin after a single dose is approximately one week; however, the effective half-life ranges from 20 to 60 hours with a mean of about 40 hours. Studies with radiolabelled drug have demonstrated that up to 92% of the orally administered dose is recovered in urine. Very little Warfarin is excreted unchanged in urine. Urinary excretion is in the form of metabolites.

Renal dysfunction. Renal clearance is considered to be a minor determinant of anticoagulant response to Warfarin. No dosage adjustment is necessary for patients with renal failure.

Hepatic dysfunction. Hepatic dysfunction can potentiate the response to Warfarin through impaired synthesis of clotting factors and decreased metabolism of Warfann

Intravenous administration.

Indications. Prophylaxis and treatment of venous thrombosis and its extension, and pulmonary embolism.

Prophylaxis and/or treatment of the thromboembolic complications associated with atrial fibrillation, coumadin is not indicated in patients with lone atrial fibrillation who are less than 60 years of age with no risk factors, e.g. previous thromboembolism (TIA, ischaemic stroke), diabetes mellitus, hypertension, and an otherwise normal heart.

Contraindications.
Threatened abortion, eclampsia and pre-eclampsia.

Inadequate laboratory facilities or unsupervised senility, alcoholism, psychosis, or lack of patient cooperation. Spinal puncture and other diagnostic or therapeutic procedures with potential for uncontrollable bleeding.

Major regional, lumbar block anaesthesia. Malignant hypertension.

Use in pregnancy. (Category D) Coumadin is contraindicated in women who are or 000may become pregnant because the drug passes through the placental barrier and may cause fatal haemorrhagic to the fetus *in utero.*

Interactions. Coumarins (mainly Warfarin) are known to interact with approximately 250 different drugs. Drugs that interact include the antiarrhythmic agents quinidine, amiodarone, propafenone and moricizine.

Some studies have shown an interaction with diuretics while others have not. Antiplatelet drugs such as aspirin at high dosages can interact whereas dipridamole does not appear to have an effect.

In the lipid lowering agents, cholestyramine and fibrates interacts with coumarins but colestipol and the HMG-CoA reductase inhibitors do not.

Antidiabetic drugs have also been shown to interact with coumarins. Regarding gastrointestinal drugs, the H_2-antagonists Cimetidine and ranitidine can interact but the proton pump inhibitors and antacids do not appear to do so.

Cardiprin 100

Composition Active, Aspirin.
Inactive. Glycine (aminoacetic acid) as a solubilising agent; saccharin. Actions Antiplatelet, antithrombotic.

Pharmacology. Metabolism of arachidonic acid via the enzyme cyclooxyygenase produces mainly thromboxane (TXA_2) in platelets, and prostacyclin (PGI_2) in the vascular endothelium. TXA_2 causes vasoconstriction and induces platelet aggregation; PGI_2 causes vasodilation and has a platelet antiaggregatory effect. Platelet cyclooxygenase is more sensitive to aspirin inhibition and can only be regenerated with the formation of new platelets. Aspirin can therefore have a selective inhibitory effect on thromboxane production and hence on platelet aggregation. *In vitro* and ex *vivo* studies have shown that at low doses (100 to 300mg) there is a differential effect between the inhibitory action of aspirin on platelet cyclooxygenase and the cyclooxygenase in the blood vessels. At these doses there is complete inhibition of platelet aggregation induced by collagen, ADP and arachidoric acid. The anti-inflammatory, antipyretic and analgesic actions of aspirin are also though to be mediated via inhibition of prostaglandins biosynthesis.

Pharmacokinetics. *Absorption.* After oral administration, aspirin is generally well absorbed from the gastrointestinal tract, partly from the stomach and mainly from the small intestine. Time to peak plasma levels is plasma levels are within 15 minutes. A small amount of aspirin is absorbed as the metabolite salicylic acid, after hydrolysis in the gastrointestinal mucosa. The rate of drug absorption is enhanced by the formulation of aspirin in a soluble form and can be significantly altered by factors delaying gastric emptying time (e.g. food).
Distribution. Salicylates are rapidly distributed through all body tissues and most transcellular fluids including plasma, spinal and synovial fluids, breast milk, saliva and peritoneal fluid. The placental barrier is readily crossed. Only small amounts of salicylate are present in sweat, bile and faeces. In normal patients the average volume of distribution is 150 mUkg.

Protein binding. Salicylate is 80 to 90% bound to plasma protein, especially albimin.
Metabolism. Aspirin is converted to salicylic acid (salicylate) in many tissues, but primarily in the gastrointestinal mucosa and the liver. Salicylate is converted mainly in the liver to three main metabolic products: salicylic acid, salicylic phenolic glucuronide and salicylic acyl glucuronide. A small amount of gentisic acid is formed. The metabolism of salicylate normally follows first order kinetics. However, after very large doses, the metabolic pathways become saturated (zero order kinetics) and small dosage increments result in large increases in aspirin levels.

Excretion. Salicylates are excreted predominantly by the kidneys. Most of an administered dose can be recovered in the urine as free salicylate (10%) or

metabolites (75% as salicyluric acid). Excretion of free salicylate is extremely variable; 85% of ingested aspirin in alkaline urine, 5% in acidic urine. Patients with impaired renal function require dosage adjustment.

Half-life. The plasma elimination half-life for aspirin is approximately 30 minutes. The half-life of salicylate is therapeutically more important and is dose dependent, increasing as the plasma concentration increases. Allow doses, the elimination half-life is two to three hours and at high dose.

ANAESTHETICS

Xylocaine Plain and Xylocaine with Adrenaline

Composition Xylocaine plain. *Active.* Lignocaine hydrochloride. *Inactive.* Sodium Chloride, sodium hydroxide to adjust pH, water for injections.

Xylocaine with adrenaline. *Active.* Lignocaine Hydrochloride, adrenaline acid tartrate. *Inactive.* Sodium chloride, sodium hydroxide, water for injections, sodium metabisulfite 0.5 mg/mL as antioxidant.

Actions Injection solutions for the production of local or regional anaesthesia. Lignocaine is classed as a membrane stabilising agent and is a local anaesthetic of the amide type.

Pharmacology. Lignocaine, 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 drugs may have similar effects on excitable membranes in the brain and myocardium. If excessive amounts of drug reach the systemic circulation rapidly, symptoms and signs of toxicity will appear, emanating mainly from the central nervous system and cardiovascular system.

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.

Pharmacokinetics. Lignocaine has a rapid onset and a medium duration of action. The onset of action is one to five minutes following infiltration and 5 to 15 minutes following other types of administration.

The addition of adrenaline considerably slows the absorption of Lignocaine, although the rate also depends on the site of injection. Peak plasma concentrations are reduced by 50% following subcutaneous injection.

Contraindications. Allergy or hypersensitivity to amide type local anaesthetics or sodium metabisulfite in solutions with adrenaline. Detection of suspected hypersensitivity by skin testing is of limited value.

Local anaesthetic techniques must not be used when there is inflammation and/or sepsis in the region of the proposed injection and/orin the presence of septicaemia.

Solutions containing adrenaline. Conditions where the production or exacerbation of tachycardia may prove fatal, e.g. thyrotoxicosis or severe heart disease, or in obstetrics when maternal blood pressure exceeds 130/80 mmHg.

Local analgesia in parts of body with compromised blood supply or supplied by end arteries, e.g. fingers, toes, nose, ears or penis. There is a possibility of producing arterial vasoconstriction and subsequent ischaemic gangrene distal to the site of injection. Intravenous regional techniques.

Known sensitivity to sympathomimetic arnines. Use in most patients with cerebral arteriosclerosis.

Precautions. 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 time restlessness, anxiety, tinnitus, dizziness, blurred vision, tremors, depression or drowsiness may be early warning signs of CNS toxicity. Elderly, young or debilitated patients, including those with advanced liver disease or severe renal dysfunction, should be given reduced doses commensurate with their age and physical condition.

Lignocaine should be given with great caution to patients with epilepsy, impaired cardiac conduction, bradycardia, severe shock or digitals intoxication. Lignocaine should also be administered with great caution to patients with impaired cardiovascular function.

Solutions with adrenaline should be used with extreme caution in patients with severe or untreated hypertension, arteriosclerotic heart disease, cerebral vascular insufficiency, heart block, advanced diabetes, poorly controlled thyrotoxicosis or any other pathological conditions that might be aggravated by the effects of adrenaline. Adrenaline may induce anginal pain in patients suffering from ischaemic heart disease.

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.

Impaired renal function. Since Lignocaine is metabolised in the liver excreted via the kidneys. the possibility of drug accumulation should be considered in patients with hepatic and/or renal impairment.

Use in lactation. Lignocaine passes into breast milk. The amount of Lignocaine appearing in breast milk from a breastfeeding woman receiving parenteral Lignocaine is unlikely to lead to a significant accumulation of parent drug in the breastfed infant.

Solutions containing adrenaline. *Drugs acting on the central nervous system.* Solutions containing adrenaline should be used with extreme caution in patients receiving MAOls or tricylic antidepressants as severe sustained hypertension my result. The effects of adrenaline may be potentiated by tricylic antidepressants. some antihistamines and thyroid hormones. Phenothiazines and butyrophenones may reduce or reverse the pressor effects of adrenaline, which may lead to a hypotensive response and tachycardia.

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

Adrenergic neuron blocking agents. Solutions containing adrenaline neuron blocking agents (e.g. guanethidine, debrisoquine, bethanidine).

Inhafational 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. trichloroethylene or other halogenated compounds.

Cardiac glycosides. Solutions with adrenaline may interact with cardiac glycosides resulting in cardiac arrhythmias.

Beta-blockers. Noncardioselective P-blockers such as propranolol enhance the pressor effects of adrenaline, which may lead to severe hypertension and bradycardia. *Quinidine.* Solutions with adrenaline may interact with quinidine, resulting in cardiac arrhythmias.

Hypogiycaemics. Adrenaline induced hyperglycaemia may lead t loss of blood sugar control in diabetic patients treated with Hypoglycaemic agents.

Adverse Reactions.
Central nervous system. CNS manifestations are excitatory and/or depressant and may be characterized by lightheadedness, nervousness, apprehension, euphoria, confusion, dizziness, drowsiness, Tinnitus, hyperacusis, blurred vision, vomiting, sensations of heat, cold or numbness, twitching, tremors, convulsions, unconsciousness, respiratory depression and/or arrest, agitation, difficulty swallowing, paraesthesia circumoral, numbness of the tongue and slurred speech.

The excitatory manifestations maybe 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 Lignocaine is usually an early sign of a high blood level of the drug and may occur as a result of rapid absorption. Monitor unconscious patients for circutatory collapse, as CNS effects may not be apparent as an early manifestation of toxicity, and may in some cases progress to frank convulsions, ultimately leading to respiratory depression and/or arrest. It is crucial to have resuscitative equipment and anticonvulsant drugs available to manage such patients.

Cardiovascular. Cardiovascular manifestations are usually depressant and are characterized by bradycardia, Hypotension and cardiovascular collapse, which may lead to cardiac arrest. Cardiac arrhythmias and hypertension have also been observed.

Methaemoglobinaemia can occur following intravenous administration.

Allergic. Allergic reactions are characterized by cutaneous lesions, urticaria, and oedema or anaphylactoid reactions/shock.

Allergy to amide type local anaesthetics is rare. Sodium metabisulfite (a sulfite), which is not included in solutions with adrenaline, may also cause allergic type reactions including anaphylactic symptoms and life-threatening or less severe asthmatic episodes in certain susceptible people. The overall prevalence of sulfite sensitivity in the general population is unknown and probably low. Sulfite sensitivity is seen more frequently in asthmatic than in non-asthmatic people. If such a reaction occurs, it should be managed by conventional means.

The detection of sensitivity by skin testing is of doubtful value.

Neurological. The incidence of adverse reactions associated with the use of local anaesthetics may be related to the total dose of local anaesthetic administered and are also dependent on the particular drug used, the route of administration and the physical status of the patient. Neurological reactions following regional nerve blocks have included persistent numbness, paraesthesia and other sensory disturbances. In a prospective review of 10,440 patients who received Lignocaine for spinal

anaesthesia, the incidences were reported to be about 3% each for positional headaches, Hypotension and backache; 2% for shivering; and less than 1 % each for peripheral nerve symptoms, nausea, respiratory inadequacy and double vision. Many of these observations may be related to local anaesthetic techniques, with or without a contribution from the local anaesthetic.

Impaired hepatic function. Although Lignocaine is metabolised by the liver, dosage reduction for local anaesthetic is probably not warranted. However, caution should be exercised with repeated doses.

Impaired renal function. Impairment of renal function is unlikely to affect Lignocaine clearance in short term (24 hours). However, toxicity due to accumulation may develop with prolonged or repeated administration.

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 anaesthetic solution (see Adverse Reactions and Precautions).

With accidental intravascular injections, the toxic effect will be obvious within one to three minutes. With Overdosage, peak plasma concentrations may not be reached for 20 to 30 minutes depending on the site of injection, and toxic signs will be delayed. Toxic reactions mainly involve the central nervous and cardiovascular systems.

In children, early signs of local anaesthetic toxicity may be difficult to detect in cases where the block is given during general anaesthesia.

Symptoms. *Acute toxicity.* CNS toxicity is a graded response with symptoms and signs of escalating severity. The first symptoms are circumoral paraesthesia, numbness of the tongue, lightheadedness, hyperacusis and Tinnitus. Visual disturbance and muscular tremors are more serious and precede the onset of generalized convulsions.

These signs must not be mistaken for neurotic behaviour.

Unconsciousness and grand mal convulsions may follow. These may last from a few seconds to several minutes. Hypoxia and hypercarbia 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. Acidosis increases the toxic effects of local anaesthetics.

Recovery is due to redistribution of the local anaesthetic drug from the central nervous system and metabolism. Recovery may be rapid unless large amounts of the drug have been injected.

Cardiovascular toxicity. Cardiovascular toxicity indicates a more *severe* situation. Hypotension, bradycardia, decreased cardiac output, heart block, arrhythmia and even ventricular arrhythmias, ventricular fibrillation and cardiac arrest may occur as a result of huge 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 a benzodiazepine or a barbiturate. In rare cases, cardiac arrest has occurred without prodromal CNS effects.

Treatment. If signs of acute systemic toxicity appear, injection of the local anaesthetic should be stopped immediately. If convulsions occur, immediate attention is required for the maintenance of a patient airway and assisted or controlled ventilation with oxygen via a positive airway pressure delivery systemic mask. Adequacy of the circulation should then be evaluated, bearing in mind that drugs used to treat convulsions depress the circulation when administered intravenously. Should convulsions persist despite adequate respiratory support, and if the status of the circulation permits, approopriate anticonvulsant medication such as an ultra short acting barbiturate (e.g.thiopentone) or a benzodiazepine (e.g. diazepam) may be administered intravenously. The clinician should be familiar with these anticonvulsant drugs prior to use of local anaesthetics. 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. If ventricular fibrillation or cardiac arrest occurs, effective cardiovascular resuscitation treatment must be instituted and maintained for a prolonged period if necessary. Optimal oxygenation and ventilation, and circulatory support as well as treatment of acidosis are of vital importance. Dialysis is of negligible value in the treatment of acute Overdosage with Lignocaine.