

Essential Drugs

Rheumatoid arthritis

Rheumatoid arthritis is a chronic progressive inflammatory disease involving joints and other tissues. It occurs in some 1–3% of adults worldwide. It is five times more common in women than in men, and its incidence increases up to the age of 60. Clinically, it is typified by a symmetrical, destructive and deforming polyarthritis affecting small and large peripheral joints. It is associated with a systemic disturbance and it is characterized by the presence of circulating antiglobulin antibodies (rheumatoid factors). The inflammatory process, which eventually results in crippling disablement, usually follows a remitting course, but it may be rapidly progressive.

The pathological basis of the condition remains uncertain, but it seems to be associated with T lymphocyte activation in genetically-predisposed individuals. The inappropriate chronic inflammatory response damages the synovial tissue lining the joints. This may first become apparent as an acute episode of pain, stiffness and symmetrical swelling of a number of peripheral joints. In other cases, the patient may complain of malaise and general fatigue well before the joints become affected. As the disease advances, muscle atrophy and joint destruction limit movement and lead to deformities. Extra-articular signs of the disease occur most commonly in the ocular, cardiovascular, renal, haemopoietic and nervous systems.

Management

The management of rheumatoid arthritis is directed to relief of symptoms, suppression of active disease and conservation or restoration of function in the affected joints.

Pain is controlled and inflammation suppressed in the first instance with acetylsalicylic acid and, when this fails, with another nonsteroidal anti-inflammatory drug (NSAID) to which a slow-acting anti-rheumatic drug (SAARD) may be added. Physical therapy, including general and specific exercises, educational programmes and psychological support are also important in preserving joint function. Surgical interventions, including total joint replacement, may ameliorate severe handicap.

NSAIDs act by inhibiting the formation of inflammatory mediator substances including prostaglandins. Many different products are available, and it remains impossible to predict which will be most effective in a given patient. It is often necessary to try several different products in sequence in order to select, on an empirical basis, one that is well tolerated and effective. Only one orally-administered NSAID should be prescribed at a time and the lowest effective dosage should be prescribed. Paracetamol is sometimes used as a supplement. It has been claimed to augment the analgesic effect. Because it has no anti-inflammatory effect, paracetamol has little other application in the management of rheumatoid arthritis.

It is advisable to use ibuprofen in the first instance because it has been associated with the lowest risk of adverse effects. Conversely, azapropazone is generally regarded as having significantly greater toxicity; it should be reserved for patients who have not responded to other NSAIDs. It should never be prescribed for patients with a history of peptic ulceration. Patients over 60 years of age requiring treatment over extended periods should not take more than 600 mg daily. Other widely-used compounds, including indometacin, ketoprofen, naproxen, diclofenac and piroxicam are associated with intermediate risk.

Gastrointestinal disturbances are the most frequently reported adverse effects. Inhibition of the cytoprotective effect of prostaglandins on the gastric mucosa can result in dyspepsia, peptic ulceration and haemorrhage. NSAIDs should consequently never be given to patients with active gastrointestinal ulceration. Disruption of the regulatory effect of prostaglandins on renal blood flow can reduce filtration and result in acute or chronic renal failure. Hepatic dysfunction, blood disorders, anaphylaxis and other allergies have also been shown to be associated with use of these drugs.

Administration of a histamine H₂-receptor blocking agent or misoprostol may enable patients who are vitally dependent on NSAIDs for effective relief of pain and stiffness to recommence treatment with an NSAID following gastrointestinal haemorrhage without high risk of recurrence.

If significant symptoms and signs of inflammation persist after several weeks of intensive NSAID therapy, use of SAARDs should be considered. These are a diverse group of substances which include aminoquinolones, sulfasalazine, penicillamine, methotrexate and organic gold compounds. They share the potential to slow the rate of functional deterioration. Treatment should be started early in the course of the disease before significant joint damage has occurred. However, specialist training is required to ensure they are used safely and to best advantage.

Chloroquine and hydroxychloroquine are relatively inexpensive, but they are not as effective as the other agents. Because long-term therapy (particularly with chloroquine) can result in retinopathy, ophthalmological examinations need to be conducted at the outset of treatment and at three-monthly intervals for as long as treatment is continued.

Sulfasalazine is effective, but it is poorly tolerated by perhaps one quarter of patients treated. Nausea, vomiting, abdominal pain, and a wide range of cutaneous reactions are frequently reported. Hepatotoxicity may also occur.

Penicillamine is no longer extensively used. It is not satisfactorily effective in the longer term, and it is associated with a high incidence of serious adverse effects including rashes, proteinuria and blood dyscrasias.

Intramuscular gold compounds are still widely used. They are among the most effective substances, and may delay or prevent progression of erosion in some patients. However, severe mucocutaneous, bone marrow and renal toxicity limit their acceptability.

Methotrexate has become the most widely prescribed drug of this group. At the dosages used for rheumatoid arthritis, it is well tolerated in the short term, but because there is a risk of hepatic and pulmonary toxicity in the longer term, patients must remain under close supervision throughout treatment.

Other immunosuppressive drugs, including azathioprine, have been used with success in resistant cases. Cyclophosphamide is reserved for patients with severe systemic complications, and particularly for life-threatening rheumatoid vasculitis.

Corticosteroids remain the most potent anti-inflammatory substances used in rheumatoid

arthritis. They are sometimes administered at lower dosage over longer periods in combination with slow-acting antirheumatic drugs. However, because of the danger of inducing Cushing's syndrome, they should be used only when other drugs have proved ineffective in controlling severe progressive disease. The smallest effective dose should be used and continuous attempts should be made to gradually reduce the daily requirement. A relatively high dose — used together with cyclophosphamide or other immunosuppressive drug — may be needed to control severe vasculitis. Otherwise, the dose should not exceed the equivalent of 10 mg prednisolone daily. A small evening dose is often effective in relieving morning stiffness in elderly patients.

ACETYLSALICYLIC ACID

tablet: 100–500 mg

suppository: 50–150 mg

Acetylsalicylic acid has anti-inflammatory, analgesic, antipyretic, antithrombotic and antirheumatic activity. In part, these effects result from inhibition of the synthesis of endogenous prostaglandins. In rheumatoid arthritis, acetylsalicylic acid relieves symptoms but it does not affect the underlying disease process.

The compound is hydrolysed partly in the gut and partly in the liver, and it is excreted mainly in the urine, both as free salicylic acid and as inactive metabolites. The plasma half-life of salicylic acid is of the order of three hours and is strongly dose-dependent.

Uses

Control of pain and suppression of inflammation in rheumatoid arthritis.

Dosage and administration

Adults: 300 mg – 1 g every 4 hours.

Administration with food or a full glass of water reduces gastric irritation.

Contraindications

- Hypersensitivity to acetylsalicylic acid.
- Bleeding disorders, anticoagulant therapy, haemorrhagic stroke, active peptic ulcer or gastritis.
- Chronic renal insufficiency.
- Haemophilia or hypoprothrombinaemia.

Precautions

Symptoms of hypersensitivity are more likely to occur in patients with asthma, urticaria or chronic rhinitis; and in patients who have developed a rash or anaphylactic phenomena after exposure to other nonsteroidal anti-inflammatory agents.

A mild haemolytic reaction may occur in patients with glucose-6-phosphate dehydrogenase deficiency.

To avoid the risk of haemorrhage, acetylsalicylic acid should not be administered within 7 days of an elective surgical operation.

Acetylsalicylic acid must at all times be kept out of the reach of children.

Use in pregnancy

Occasional use of acetylsalicylic acid carries no apparent risk during early pregnancy. However, it should not be taken during the last three months of pregnancy since it has been reported to prolong labour and contribute to perinatal bleeding in the mother and child.

Adverse effects

Hypersensitivity reactions, which may occasionally be severe, include urticaria, angio-oedema, pruritus, and anaphylactic phenomena.

Gastrointestinal effects, which include dyspepsia, heartburn, epigastric distress and nausea, are common and sometimes severe. Gastrointestinal bleeding can result from acute mucosal erosion or reactivation of peptic ulceration. Bleeding is commonly occult but occasionally profuse and even fatal.

Inhibition of platelet aggregation may result in prolongation of bleeding time. Leukopenia, thrombocytopenia, purpura and pancytopenia have rarely been reported.

Hearing disturbances such as tinnitus, vertigo and mental confusion may occur with high dosage.

Drug interactions

Concomitant use of NSAIDs increases the incidence of adverse gastrointestinal effects but does not enhance the therapeutic effect.

The therapeutic action of anticoagulants may be potentiated.

Conversely, the efficacy of uricosuric agents and spironolactone may be reduced.

Co-administration of acetylsalicylic acid and corticosteroids greatly increases the risk of gastrointestinal bleeding.

Overdosage

Acute ingestion of 20–25 g by an adult can be lethal and smaller quantities can cause serious toxicity.

Characteristic early symptoms of overdosage include nausea and vomiting, abdominal pain and tinnitus which may ultimately progress to deafness. These are followed by flushing, sweating and hyperventilation with respiratory alkalosis. In severe cases, metabolic acidosis and coma supervene.

Activated charcoal is the preferred treatment for salicylate poisoning with an initial dose of 50 g for adults which can be repeated every four hours until symptomatic improvement occurs. Hyperthermia, dehydration, acidosis and potassium deficiency should be corrected symptomatically.

Whole blood transfusion may be necessary in the event of spontaneous haemorrhage. No advantage is obtained by administering vitamin K supplements.

Sodium bicarbonate may be administered to alkalinize the urine and to promote urinary excretion. However, when the serum salicylate concentration is dangerously high or when serious complications develop, such as unresponsive acidosis, impaired urinary output, pulmonary oedema, persistent seizures or coma, haemodialysis may offer the only hope of survival.

Storage

Acetylsalicylic acid tablets should be kept in tightly closed containers. If an odour of acetic acid is perceptible on opening the container, the tablets should be discarded. Suppositories should be stored below 15° C.

IBUPROFEN

tablet: 200 mg, 400 mg, 600 mg

suppository: 500 mg

oral solution: 20 mg/ml

Ibuprofen is a nonsteroidal anti-inflammatory agent (NSAID) with analgesic, anti-inflammatory and antipyretic actions. It acts by inhibiting prostaglandin synthesis. In rheumatoid arthritis, ibuprofen and other NSAIDs relieve symptoms but they do

not affect the underlying disease process. Whereas the analgesic action of a single dose lasts 6–8 hours, the maximum benefit in patients with rheumatoid arthritis may be obtained only after several months of regular use. Whenever possible, the decision to start treatment with an NSAID and the subsequent monitoring of its effects should be undertaken by a specialist rheumatologist.

Ibuprofen is largely metabolized in the liver. It has a plasma half-life of 2 hours and is excreted by the kidneys.

Uses

To control pain and suppress inflammation in rheumatoid arthritis.

Dosage and administration

Adults: 400–3600 mg daily in divided doses, as determined by the response.

Administration with food or water may reduce gastric irritation. Rectal absorption is slow and incomplete but suppositories may be of value in patients unable to take oral dosage forms

Contraindications

Hypersensitivity to acetylsalicylic acid or any NSAID including asthma, angioedema, urticaria or rhinitis. Peptic ulceration.

Precautions

Particularly careful consideration should be given to using NSAIDs in the elderly and in patients with a history of peptic ulcer or bleeding disorder. Dyspepsia may be reduced by taking each dose together with food or milk.

Patients with impaired renal function should be monitored carefully throughout treatment.

Use in pregnancy

Safe use in pregnancy has not been established. Ibuprofen should be used only when the need of the mother outweighs any possible risk to the fetus.

Adverse effects

Among the NSAIDs, ibuprofen is associated with the least overall risk of adverse effects.

Gastrointestinal adverse reactions including dyspepsia, peptic ulceration, and haemorrhage usually necessitate withdrawal of treatment (see p. 35).

Hypersensitivity reactions (particularly angioedema, bronchospasm and rash), dizziness, headache and

some cases of reversible amblyopia have been reported.

Ibuprofen inhibits platelet aggregation and bleeding time is prolonged.

Reversible acute renal failure has been provoked. Rarely, papillary necrosis or interstitial fibrosis has been reported.

Rarely reported reactions include aseptic meningitis, exacerbation of connective-tissue disorders, fluid retention and hepatic damage.

Drug interactions

Concomitant use of acetylsalicylic acid or other NSAIDs increases the incidence of gastrointestinal adverse effects but does not enhance the therapeutic effect.

Overdosage

Dizziness, nystagmus, apnoea, and hypotension leading to loss of consciousness are symptoms of overdosage. Gastric lavage and supportive measures are necessary. Most patients recover without serious sequelae.

Storage

Preparations of ibuprofen should be stored in well-closed containers, protected from light.

INDOMETACIN

capsule or tablet: 25 mg

capsule: 50 mg

suppository: 100 mg

oral solution: 5 mg/ml

injection: 50 mg/10 ml

Indometacin, a nonsteroidal anti-inflammatory agent (NSAID) with analgesic, anti-inflammatory and antipyretic effects. Its action in rheumatoid arthritis is qualitatively identical to that of ibuprofen.

It is rapidly and almost completely absorbed from the gastrointestinal tract. The plasma half-life is 5–10 hours. It is metabolized in the liver and excreted as metabolites and unchanged drug in the bile and urine.

Uses

To control pain and suppress inflammation in rheumatoid arthritis.

Dosage and administration

Adults: 100–200 mg daily in divided doses

Contraindications, precautions, use in pregnancy and adverse effects

As for ibuprofen.

Indometacin has been claimed to have more severe effects on the central nervous system than other NSAIDs. It may aggravate psychiatric disorders, epilepsy or parkinsonism. Severe headache, depression and disorientation have been described with higher doses.

Drug interactions

Concomitant use of acetylsalicylic acid or other NSAIDs increases the incidence of adverse gastrointestinal effects but does not enhance the therapeutic effect.

Serum concentrations of lithium are elevated when given with indometacin.

Indometacin may reduce the diuretic and anti-hypertensive effects of furosemide, thiazides and potassium-sparing diuretics.

Overdosage

Nausea, vomiting, headache, dizziness, mental confusion, disorientation and lethargy are symptoms of acute overdosage.

Gastric lavage and supportive treatment is necessary.

Storage

Preparations should be stored in tightly closed containers, protected from light.

CHLOROQUINE

tablet: 100 mg, 150 mg base (as phosphate or sulfate)

Chloroquine is a 4-aminoquinoline antimalarial drug. In common with other slow-acting anti-rheumatic drugs, chloroquine gradually improves symptoms and suppresses serological markers of active rheumatoid arthritis. It also slows the progression of the disease, but it is uncertain whether it modifies the ultimate outcome.

It is absorbed efficiently from the gastrointestinal tract and peak plasma concentrations occur within 2–3 hours. The drug and its metabolites can be detected in the plasma for up to 2 months and in the urine for up to 4 months after a single dose.

Uses

Slowing of disease progression in rheumatoid arthritis

Dosage and administration

Adults: 3.5 mg/kg up to a maximum of 250 mg daily.

Contraindications

Known hypersensitivity.

Precautions

Baseline renal function should be measured, since the need for dosage reduction should be considered in patients with renal impairment.

Hepatic function should be carefully monitored throughout treatment in patients with pre-existing hepatic disease.

An ophthalmic examination should be carried out before treatment is started and subsequently at three monthly intervals to detect dose-related deposition of pigment and scotomata. In patients with normal renal function ocular toxicity rarely occurs at daily dosages less than 3.5 mg/kg.

Use in pregnancy

No untoward effects have been demonstrated, but treatment is best deferred, when possible, until after the first trimester of pregnancy.

Adverse effects

Transient headaches and gastrointestinal symptoms are occasionally troublesome.

Corneal deposits are common and reversible; accommodation defects and irreversible retinopathy are unlikely to occur at recommended dosages.

Chloroquine may precipitate a severe exacerbation of psoriasis.

Overdosage

Acute chloroquine poisoning is often fatal; the lethal dose may be as low as 50 mg chloroquine base/kg. Nausea, vomiting and drowsiness, which occur rapidly, are followed by slurring of speech, agitation, visual impairment, breathlessness due to pulmonary oedema, cardiac dysrhythmias, convulsions and coma.

Emesis must be induced, or gastric lavage undertaken, as rapidly as possible if the patient is seen within a few hours of ingestion. Otherwise

treatment is symptomatic and is directed particularly to sustaining cardiovascular and respiratory function. Diazepam may help to control convulsions.

Storage

Tablets should be kept in well-closed containers, protected from light and moisture.

PENICILLAMINE

capsule or tablet: 250 mg

Penicillamine is a monothiol chelating agent which is a degradation product of all penicillins. Its mechanism of action in the treatment of rheumatoid arthritis may be related to inhibition of collagen formation. Its effect in slowing the progression of the disease is similar to that of intramuscular gold. However, it is less effective in the longer term, and it is associated with a higher incidence of adverse effects.

It is readily absorbed from the gastrointestinal tract, metabolized in the liver, and excreted in the urine and faeces as inactive disulfides.

Uses

Treatment of active rheumatoid arthritis unresponsive to acetylsalicylic acid and NSAIDs.

Dosage

Adults: 125 mg daily for one month and subsequently increased to 250 mg, 500 mg, and 750 mg daily at four to six week intervals.

Contraindications

History of penicillamine-induced agranulocytosis, aplastic anaemia or severe thrombocytopenia. Renal impairment. Lupus erythematosus. Pregnancy.

Precautions

Patients should be monitored closely for allergic reactions. Patients hypersensitive to penicillins may react similarly to penicillamine but cross-sensitivity appears to be rare.

Thrombocytopenia, which is common and often dose related, can occur early and is sometimes severe. Patients should be instructed to report immediately symptoms of fever, sore throat or unusual bleeding.

Analysis of urine for presence of protein should be performed at weekly intervals and subsequently every four weeks.

Adverse reactions

Allergic reactions occur in about one-third of patients. Most common is a generalized skin rash. Rarely, myositis, myasthenia or drug-induced lupus erythematosus has been reported.

Gastrointestinal effects include anorexia, nausea, epigastric pain and dyspepsia. Taste impairment is common.

Adverse haematological reactions include leukopenia, thrombocytopenia and bone marrow depression.

Proteinuria, a sign of immune complex nephritis, sometimes resolves on adjustment of dosage.

Drug interactions

The absorption of penicillamine is reduced by iron.

Storage

Tablets and capsules should be stored in tightly closed containers.

SULFASALAZINE

tablet: 500 mg

Sulfasalazine is composed of sulfapyridine and 5-aminosalicylic acid joined by a diazo bond. When administered in enteric-coated formulations, it is split in the colon into its component parts.

Uses

Treatment of active rheumatoid arthritis unresponsive to acetylsalicylic acid and NSAIDs. It is probably less effective than intramuscular gold or penicillamine, but it is better tolerated.

Dosage and administration

Adults: 500 mg daily in an enteric-coated formulation-increased by 500 mg increments every 2-4 weeks to a total dose of 2-4 g daily. Maintenance dose is generally 2 g daily.

Contraindications

Known hypersensitivity to sulfonamides or salicylates. Severe hepatic impairment.

Precautions

The blood count should be monitored at the start of treatment and at monthly intervals thereafter.

Liver function tests should be carried out at regular intervals.

Adverse effects

Almost 25% of patients have to discontinue therapy due to toxicity.

Nausea, headache, loss of appetite and fever are common adverse effects.

Folate deficiency is common; adequate dietary intake should be assured.

Hypersensitivity reactions include generalized skin rashes and urticaria and, occasionally, life-threatening Stevens-Johnson syndrome or anaphylaxis.

Patients with glucose-6-phosphate dehydrogenase deficiency are at particular risk of haemolytic anaemia.

Bone-marrow depression occurs rarely; toxic hepatitis has been reported; reversible oligospermia and male infertility have been described.

Use in pregnancy

Safe use in pregnancy has not been demonstrated. It should be used only when the need of the mother outweighs any possible harm to the fetus.

Drug interaction

Sulfasalazine can impair the absorption of digoxin and an interval of 2–3 hours should elapse between oral administration of these drugs.

Overdosage

Emesis and gastric lavage may be of value within a few hours of overdosage. Otherwise, treatment is supportive.

Storage

Tablets should be stored in well-closed containers.

METHOTREXATE

tablet: 2.5 mg (as sodium salt)

powder for injection: 50 mg (as sodium salt) in vial

Methotrexate is a folic acid antagonist. In the doses used in rheumatoid arthritis it does not produce systemic immunosuppression.

Absorption from the gastrointestinal tract is variable. Some patients respond better to intramuscular therapy. Clinical improvement usually appears earlier than with gold or penicillamine.

Uses

Treatment of severe active rheumatoid arthritis.

Dosage and administration

Adults: 7.5–15 mg weekly either orally or intramuscularly.

Contraindications

Pre-existing blood dyscrasias, chronic liver disease, pregnancy.

Precautions

A complete blood count and liver function test should be performed before starting therapy and every four weeks for the first year and thereafter at three-monthly intervals.

Renal function tests should be measured every three months.

Adverse effects

Unwanted effects occur commonly, but are usually mild or transient in the dosage recommended for rheumatoid arthritis.

Gastrointestinal adverse effects include stomatitis, nausea, vomiting and abdominal pain.

Pulmonary hypersensitivity presents with cough, fever and dyspnoea. Most patients recover on withdrawal of treatment, but some develop pulmonary fibrosis. The risk of cumulative hepatic toxicity is more remote. Some rheumatologists advise liver biopsy to detect possible early signs of fibrosis and cirrhosis after a cumulative dose of 1.5 g (about three years' treatment).

Bone-marrow suppression is rare at the doses used in rheumatoid arthritis.

Drug interactions

Concomitant administration of tetracycline and chloramphenicol decreases methotrexate absorption.

Toxicity may be increased by concomitant administration of salicylate or another nonsteroidal anti-inflammatory agent, and by use of other antifolate compounds.

Storage

Tablets and powder for injection should be stored in well-closed containers, protected from light.

PREDNISOLONE

tablet: 5 mg, 25 mg

injection: 5 mg (as sodium phosphate or succinate) in vial

Prednisolone is a synthetic glucocorticoid with minimal mineralocorticoid properties. Its therapeutic effect results from inhibition of macrophage accumulation, suppression of capillary-wall permeability and oedema formation and reduction of fibroblast proliferation and collagen deposition. It is readily absorbed from the gastrointestinal tract, is extensively protein bound and has a plasma half-life of about 8 hours.

Uses

Suppression of active rheumatoid arthritis in patients unresponsive to any other treatment.

Dosage and administration

The lowest dosage to produce an acceptable clinical response should be used. Dosage should not exceed 7.5–10 mg daily.

Contraindications

Prednisolone should not be used unless other anti-inflammatory and disease-modifying drugs have proved unsuccessful. Known hypersensitivity. Active peptic ulcer.

Prednisolone should not be used in patients with presumed viral or bacterial infections because corticosteroids increase susceptibility to, and mask the symptoms of infection.

Precautions

Patients must understand the importance of following dosage instructions rigorously. Should they feel unexpectedly unwell, they should immediately seek medical advice. If this is not possible, they should double the next scheduled dose of corticosteroid.

The response of the pituitary-adrenal axis to stress is reduced and may remain depressed for many months after withdrawal. Dosage may need to be doubled or reinstated temporarily during this period if infection occurs.

Bone pain, and particularly backache, may be indicative of osteoporosis.

Use in pregnancy

Corticosteroids should not be administered during pregnancy unless the need outweighs any possible risk of harm to the fetus. Adrenal development may be impaired and a relationship with cleft palate and other abnormalities may exist, particularly in the case of fluorinated compounds. Dosage should be kept as low as possible, but requirements may be raised slightly in replacement therapy as a result of increased binding of corticosteroids to plasma proteins during pregnancy.

Corticosteroids are secreted into breast milk and breast-feeding should be avoided.

Adverse effects

The adverse effects of long-term systemic corticosteroids include osteoporosis, cataracts, poor wound healing, gastrointestinal bleeding, hyperglycaemia, hypertension, and increased risk of infection. Quiescent tuberculosis may be reactivated, and psoriasis may be exacerbated on withdrawal of therapy.

Drug interactions

Hepatic enzyme inducers including phenobarbitone, phenytoin and rifampicin may accelerate the metabolism of prednisolone.

The response to oral anticoagulants may be altered. Inhibition is characteristic, but isolated reports of potentiation are on record.

The incidence of gastrointestinal ulceration is increased if acetylsalicylic acid or nonsteroidal anti-inflammatory drugs are administered concomitantly.

The risk of hypokalaemia is increased when corticosteroids are taken concomitantly with potassium-losing diuretics.

Overdosage

In the event of a single large overdosage, specific treatment is unlikely to be required. Symptomatic treatment is indicated for reactions due to chronic poisoning.

Storage

Tablets should be stored in well-closed containers. Prednisolone sodium phosphate injection should be protected from light. Freezing should be avoided.

**The information in this section is subject to consultation prior to definitive publication.
Comments, which are invited at this stage, should be referred to:**

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