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RHEUMACIN & RHEUMACIN SR

Indomethacin



Presentation

25 mg Capsules: white OP body, white OP cap, size 3. Contents a white powder.

50 mg Capsules: white OP body, white OP cap, size 2. Contents a white powder.

75 mg SR Capsules: clear colourless body, clear yellow cap, size 2. Contents small off-white spheres.

Uses

Actions

RHEUMACIN (indomethacin) is a highly effective nonsteroidal anti-inflammatory medicine with marked analgesic and antipyretic properties.

INDOMETHACIN is a potent inhibitor of prostaglandin synthesis *in vitro*. Concentrations are reached during therapy which have been demonstrated to have an effect *in vivo* as well.

INDOMETHACIN has been shown to be effective anti-inflammatory agent, appropriate for long-term use in rheumatoid arthritis, ankylosing spondylitis, and osteoarthritis.

INDOMETHACIN affords relief of symptoms; it has not been shown to alter the progressive course of the underlying disease.

INDOMETHACIN has been found effective in relieving the pain, reducing the fever, swelling, redness, and tenderness of acute gouty arthritis.

The prostaglandin-inhibitory effect of INDOMETHACIN has been shown to be useful in the relief of pain and associated symptoms of primary dysmenorrhoea.

Anti-inflammatory Action

The anti-inflammatory activity of INDOMETHACIN was first demonstrated in animals, measuring the ability of the compound to inhibit either granuloma formation or oedema induced by subplantar injection of carrageenin in rats. The latter appears to correlate well with antirheumatic activity in humans. Assays of relative potency indicated that INDOMETHACIN was more potent than acetylsalicylic acid, phenylbutazone or hydrocortisone; the potency ratios differed with the test employed.

The inhibition of carrageenin-induced oedema by INDOMETHACIN is specific; the compound failed to inhibit oedema induced by a variety of agents other than carrageenin, nor did it reduce oedema if the medicine was administered after the oedema had been established.

As with other anti-inflammatory agents, the mechanism of action of INDOMETHACIN is unknown. INDOMETHACIN is fully active in the absence of the adrenals and the activity is readily demonstrable by direct application of the compound to the site of action. Unlike anti-inflammatory steroids, INDOMETHACIN in intact animals did not affect the size of the adrenals or the thymus, nor did it retard gain in body weight; these are sensitive indications of adrenal activation. The anti-inflammatory activity of combinations of INDOMETHACIN and a steroid was that of either medicine alone in comparable doses.

Experiments have shown INDOMETHACIN to have a favourable effect upon adjuvant-induced polyarthritis in rats; it was more active than phenylbutazone or acetylsalicylic acid in suppressing the delayed manifestations of disseminated arthritis. This response is said to correlate well with clinical antiarthritic activity.

Antipyretic Activity

The antipyretic activity of INDOMETHACIN has been demonstrated in rabbits and rats injected with bacterial pyrogen, and in the classical yeast-induced fever assay in rats.

A direct comparison of peak antipyretic activity in the yeast fever test showed INDOMETHACIN to be about nine times as potent as aminopyrine, 24 times as potent as phenylbutazone, and 43 times as potent as acetylsalicylic acid.

The antipyretic activity of INDOMETHACIN has been confirmed clinically by observations in patients with a variety of febrile conditions.

Analgesic Activity

INDOMETHACIN is active in animal tests designed to assay analgesic activity of non-narcotic analgesics. Moderate doses raise the response threshold when pressure is applied to the yeast-inflamed foot of the rat, but do not affect responses to thermal stimuli, or to pressure on a non-inflamed foot. Qualitatively, INDOMETHACIN behaves like an analgesic of the anti-inflammatory/antipyretic type typified by the salicylates, and not of the narcotic type typified by morphine.

When single oral doses of INDOMETHACIN were assayed in the inflamed foot assay, the compound was found to be about 28 times as potent as acetylsalicylic acid and about 14 times as potent as phenylbutazone.

Pharmacokinetics

INDOMETHACIN is well absorbed after oral administration in all animals. In dogs, monkeys and rats, peak plasma levels after an oral dose occur within 0.5 to 2 hours.

The route of excretion is related to the species of animal and is independent of the route of administration or size of dose. Nearly all the compound or medicine-related metabolites could be recovered in urine and faeces. The rabbit eliminates INDOMETHACIN almost entirely in the urine, while the dog excretes nearly all the compound in the faeces. The rat, guinea pig, and monkey eliminate it by both routes.

In rabbits, rats, guinea pigs, and monkeys some INDOMETHACIN is metabolised by deacylation or demethylation and the metabolites are excreted as such or as the glucuronide conjugate.

Clinical Studies

Prostaglandins sensitise afferent nerves and potentiate the action of bradykinin in inducing pain in animal models. Moreover, prostaglandins are known to be among the mediators of inflammation. Since INDOMETHACIN is an inhibitor of prostaglandin synthesis, the mode of action may be due to a decrease of prostaglandins in peripheral tissues.

In patients treated with INDOMETHACIN for rheumatoid arthritis and osteoarthritis, the anti-inflammatory action of INDOMETHACIN has been shown by reduction in joint swelling, reduction in pain, reduction in duration of morning stiffness, reduction in disease activity as assessed by both the investigator and patient; and by improved functional capacity as demonstrated by an increase in grip strength, and a decrease in time to walk 50 feet.

Following single oral doses of Capsules INDOMETHACIN 25 mg or 50 mg, INDOMETHACIN is readily absorbed, attaining peak plasma concentrations of approximately 1 and 2 mcg/ml, respectively, at about 2 hours. Orally administered Capsules INDOMETHACIN are virtually 100% bioavailable, with 90% of the dose absorbed within 4 hours.

Capsules INDOMETHACIN SR 75 mg are designed to release 25 mg of the medicine initially and the remaining 50 mg over approximately 12 hours (90% of dose absorbed by 12 hours). When measured over a 24 hour period, the cumulative amount and time-course of INDOMETHACIN absorption from a single Capsule INDOMETHACIN SR are comparable to those of 3 doses of 25 mg Capsules INDOMETHACIN given at 4-6 hour intervals.

Plasma concentrations of INDOMETHACIN fluctuate less and are more sustained following administration of Capsules of INDOMETHACIN SR than following administration of 25 mg Capsules INDOMETHACIN given at 4-6 hour intervals. In multiple-dose comparisons, the mean daily steady-state plasma level of INDOMETHACIN attained with daily administration of Capsules INDOMETHACIN SR 75 mg was indistinguishable from that following Capsules INDOMETHACIN 25 mg given at 0, 6 and 12 hours daily. However, there was a significant difference in INDOMETHACIN plasma levels between the two dosage regimens, especially after 12 hours.

Controlled clinical studies in patients with osteoarthritis have shown that one Capsule INDOMETHACIN SR was clinically comparable to one 25 mg Capsule INDOMETHACIN t.i.d; and in controlled clinical studies in patients with rheumatoid arthritis, one Capsule INDOMETHACIN SR taken in the morning and one in the evening were clinically indistinguishable from one 50 mg Capsule INDOMETHACIN t.i.d.

INDOMETHACIN is eliminated via renal excretion, metabolism, and biliary excretion. INDOMETHACIN undergoes appreciable enterohepatic circulation. The mean half-life of INDOMETHACIN is estimated to be about 4.5 hours. With a typical therapeutic regimen of 25 or 50 mg t.i.d, the steady-state plasma concentrations of INDOMETHACIN are an average 1.4 times those following the first dose.

INDOMETHACIN exists in the plasma as the parent medicine and its desmethyl, desbenzoyl, and desmethyl-desbenzoyl metabolites, all in the unconjugated form. About 60% of an oral dosage is recovered in urine as medicine and metabolites (26% as INDOMETHACIN and its glucuronide), and 33% is recovered in faeces (1.5% as INDOMETHACIN).

About 90% of INDOMETHACIN is bound to protein in plasma over the expected range of therapeutic plasma concentrations.

Indications

RHEUMACIN is indicated in active stages of:

1. Rheumatoid arthritis
2. Osteoarthritis
3. Degenerative joint disease of the hip
4. Ankylosing spondylitis
5. Acute gouty arthritis

It is also included for:

Acute musculoskeletal disorders, such as bursitis, tendonitis, synovitis, tenosynovitis, capsulitis of the shoulder, sprains and strains.

Low back pain (commonly referred to as lumbago).

Fever (as a short-term adjunct to specific therapy).

Inflammation, pain, trismus and swelling following dental procedures.

Inflammation, pain and swelling following orthopaedic surgical procedures and nonsurgical procedures associated with reduction and immobilisation of fractures or dislocations.

Pain and associated symptoms of primary dysmenorrhoea.

Dosage and Administration

RHEUMACIN is available in the following dosage forms to provide maximum flexibility and interchangeability:

Capsules: 25 mg or 50 mg for oral administration.

Capsules-SR: 75 mg provide 25 mg of free INDOMETHACIN for immediate dissolution and 50 mg of time release coated pellets.

The recommended dosage of INDOMETHACIN is 50 mg to 200 mg daily in divided doses and should be adjusted to the individual patient's response and tolerability to the medicine.

Unlike some other potent antirheumatic agents, an initial high "loading" dose of INDOMETHACIN is not necessary. In chronic rheumatic disorders, initiating therapy with low doses, increasing gradually when necessary, and continuing for an adequate period (up to one month is recommended) will produce maximum benefit and minimise adverse reactions.

In patients with persistent night pain and/or morning stiffness, a dose of up to 100 mg at bedtime may be helpful in affording relief. It is rarely necessary to exceed a dosage of 200 mg per day.

In treatment of acute gouty arthritis, the recommended daily dosage is 150 mg to 200 mg in divided doses until all symptoms and signs subside. Capsules INDOMETHACIN SR are not recommended for use in acute gouty arthritis. In primary dysmenorrhoea, the recommended dosage is 75 mg daily as a single or divided dose, starting at the onset of cramps or bleeding and continuing for as long as symptoms usually last.

To minimise the possibility of gastrointestinal disturbance, it is recommended that oral INDOMETHACIN be taken with food or an antacid.

Elderly patients are more prone to adverse effects. Caution must be taken with dosage in this group, and also in patients with renal impairment.

After assessing the risk/benefit ratio in each individual patient, the lowest effective dose for the shortest possible duration should be used.

Contraindications

INDOMETHACIN should not be used in:

Patients who are hypersensitive to any component of this product.

Patients in whom acute asthmatic attacks, urticaria, or rhinitis are precipitated by acetylsalicylic acid or other non-steroidal anti-inflammatory agents.

As with other anti-inflammatory agents, INDOMETHACIN may mask the signs and symptoms of peptic ulcer. Because INDOMETHACIN may cause peptic ulceration or irritation of the gastrointestinal tract, it should not be given to patients with active peptic ulcer or with a recurrent history of gastrointestinal ulceration.

Use in Pregnancy and in Nursing Mothers

Administration of INDOMETHACIN is not recommended during pregnancy or in nursing mothers. INDOMETHACIN is excreted in breast milk.

The known effects of medicines of this class on the human foetus during the third trimester of pregnancy are closure of the ductus arteriosus, platelet dysfunction with resultant bleeding, renal dysfunction or failure with oligohydramnios, gastrointestinal bleeding or perforation and myocardial degenerative changes.

Warnings and Precautions

As advancing years appear to increase the possibility of side effects, INDOMETHACIN should be used with greater care in the elderly.

Safe conditions for use in children under two years of age have not been established. Children should be monitored closely and periodic evaluations of liver function should be performed at appropriate intervals. Cases of hepatotoxicity including fatalities have been reported.

Patients on long term therapy should have blood chemistry and renal function checked periodically. Treatment should immediately be withdrawn if any impairment becomes evident. NSAIs should be administered to patients with impaired liver function only in cases of necessity.

The propensity of NSAIs to interact with other medicines may influence the treatment of other conditions.

Central Nervous System Effects

Headache, sometimes accompanied by dizziness or light headedness, may occur usually early in treatment with INDOMETHACIN. Although the severity of these effects rarely requires discontinuing therapy, if headache persists despite dose reduction, INDOMETHACIN therapy should be discontinued. Patients should be warned they may experience dizziness and in this event should not operate motor vehicles and should avoid potentially dangerous activities which require alertness.

INDOMETHACIN should be used with caution in patients with psychiatric disturbances, epilepsy or parkinsonism, since it may, in some instances, tend to aggravate these conditions.

Gastrointestinal events

All NSAIDs can cause gastrointestinal discomfort and rarely serious, potentially fatal gastrointestinal effects such as ulcers, bleeding and perforation, which may increase with dose or duration of use, but can occur at any time without warning. Upper GI ulcers, gross bleeding, or perforation caused by NSAIDs occur in approximately 1% of patients treated with for 3-6 months and in about 2-4 patients treated for one year. These trends continue with longer duration of use, increasing the likelihood of developing a serious GI event at some time during the course of therapy. However, even short-term therapy is not without risk.

Caution is advised in patients with risk factors for gastrointestinal events who may be at greater risk of developing serious gastrointestinal events, e.g. the elderly, those with a history of serious gastrointestinal events, smoking and alcoholism. When gastrointestinal bleeding or ulceration occurs in patients receiving NSAIDs, the drug should be withdrawn immediately. Doctors should warn patients about the signs and symptoms of serious gastrointestinal toxicity.

The concurrent use of aspirin and NSAIDs also increase the risk of serious gastrointestinal adverse events.

The gastrointestinal effects may be reduced by giving the oral formulations of the medicine immediately after meals, or with food, or with antacids.

Cardiovascular Thrombotic Events

Observational studies have indicated that non-selective NSAIDs may be associated with an increased risk of serious cardiovascular events, including myocardial infarction and stroke, which may increase with dose or duration of use. Patients with cardiovascular disease or cardiovascular risk factors may also be at greater risk. To minimise the potential risk of an adverse cardiovascular event in patients taking an NSAID, especially in those with cardiovascular risk factors, the lowest effective dose should be used for the shortest possible duration (see Dosage and Administration).

There is no consistent evidence that the concurrent use of aspirin mitigates the possible increased risk of serious cardiovascular thrombotic events associated with NSAID use.

Hypertension

NSAIDs may lead to the onset of new hypertension or worsening of pre-existing hypertension, and patients taking anti-hypertensives with NSAIDs may have an impaired anti-hypertensive response. Caution is advised when prescribing NSAIDs to patients with hypertension. Blood pressure should be monitored closely during initiation of NSAID treatment and at regular intervals thereafter.

Heart failure

Fluid retention and oedema have been observed in some patients taking NSAIDs; therefore caution is advised in patients with fluid retention or heart failure

Severe Skin Reactions

NSAIDs may very rarely cause serious cutaneous adverse events such as exfoliative dermatitis, toxic epidermal necrolysis (TEN) and Stevens-Johnson syndrome (SJS), which can be fatal and occur without warning. These serious adverse events are idiosyncratic and are independent of dose or duration of use. Patients should be advised of the signs and symptoms of serious skin reactions and to consult their doctor at the first appearance of a skin rash or any other sign of hypersensitivity.

Infections

In common with other anti-inflammatory/analgesic/antipyretic medicines, INDOMETHACIN possesses the potential for masking the signs and symptoms which ordinarily accompany infectious disease. The physician should be alert to this possibility to avoid undue delay in initiating appropriate treatment of the infection. INDOMETHACIN should be used with caution in patients with existing, but controlled, infection.

Ocular Effects

Corneal deposits and retinal disturbances, including those of the macula, have been observed in some patients who had received prolonged therapy with INDOMETHACIN.

The prescribing physician should be alert to the possible association of these changes and therapy with INDOMETHACIN; however, similar eye changes have been observed in patients with rheumatoid arthritis who have not received INDOMETHACIN. It is advisable to discontinue therapy if such changes are observed. Blurred vision may be a significant symptom and warrants a thorough ophthalmological examination. Since these changes may be asymptomatic, ophthalmological examination at periodic intervals is desirable in patients where therapy is prolonged.

Platelet Aggregation

INDOMETHACIN, like other non-steroidal anti-inflammatory agents, can inhibit platelet aggregation. This effect is of shorter duration than that seen with acetylsalicylic acid and usually disappears within 24 hours after discontinuation of INDOMETHACIN. INDOMETHACIN has been shown to prolong bleeding time (but within the normal range) in normal subjects. Because this effect may be exaggerated in patients with underlying haemostatic defects, INDOMETHACIN should be used with caution in persons with coagulation defects.

Renal Function

As with other non-steroidal anti-inflammatory medicines, there have been reports of acute interstitial nephritis with haematuria, proteinuria, and occasionally nephrotic syndrome in patients receiving long-term administration of INDOMETHACIN.

In patients with reduced renal blood flow where renal prostaglandins play a major role in maintaining renal perfusion, administration of a non-steroidal anti-inflammatory agent may precipitate overt renal decompensation.

Patients at greatest risk of this reaction are those with renal or hepatic dysfunction, diabetes mellitus, advanced age, extracellular volume depletion, congestive heart failure, sepsis, or concomitant use of any nephrotoxic medicine. A non-steroidal anti-inflammatory medicine should be given with caution and renal function should be monitored in any patient who may have reduced renal reserve. Discontinuation of non-steroidal anti-inflammatory therapy is usually followed by recovery to the pretreatment state.

Increases in serum potassium concentration, including hyperkalaemia, have been reported, even in some patients without renal impairment. In patients with normal renal function, these effects have been attributed to a hyporeninemic-hypoaldosteronism state (see Interactions).

Since INDOMETHACIN is eliminated primarily by the kidneys, patients with significantly impaired renal function should be closely monitored; a lower daily dosage should be used to avoid excessive medicine accumulation.

Laboratory Tests

As with other non-steroidal anti-inflammatory medicines, borderline elevations of one or more liver tests may occur. Significant (3 times the upper limit of normal) elevations of SGPT (ALAT) or SGOT (ASAT) occurred in controlled clinical trials in less than 1% of patients receiving therapy with non-steroidal anti-inflammatory medicines. A patient with symptoms and/or signs suggesting liver dysfunction, or in whom an abnormal liver test has occurred, should be evaluated for evidence of the development of more severe hepatic reaction while on therapy with INDOMETHACIN.

If abnormal liver tests persist or worsen, if clinical signs and symptoms consistent with liver disease develop, or if systemic manifestations occur (eg. eosinophilia, rash, etc) therapy should be discontinued.

False-negative results in the dexamethasone suppression test (DST) in patients being treated with INDOMETHACIN have been reported. Thus, results of the DST should be interpreted with caution in these patients.

Animal Toxicology

In an 81-week chronic oral toxicity study in the rat at doses up to 1 mg/kg/day, INDOMETHACIN had no tumourigenic effect.

INDOMETHACIN produced no neoplastic or hyperplastic changes related to treatment in lifetime carcinogenic studies in the rat (dosing period 73-110 weeks) and the mouse (dosing period 62-88 weeks) at doses up to 1.5 mg/kg/day.

INDOMETHACIN at dosage levels up to 0.5 mg/kg/day did not have any mutagenic effect in *in vitro* bacterial tests (Ames test and *E. coli* with or without metabolic activation) and a series of *in vivo* tests including the host-mediated assay, sex-linked recessive lethals in *Drosophila* and the micronucleus test in mice. INDOMETHACIN had no effect on fertility in mice in a two-generation reproduction study or a two-litter reproduction study in rats.

Adverse Effects

Central Nervous System

Central nervous system side effects associated with INDOMETHACIN are headache, dizziness, light-headedness, depression, vertigo and fatigue (including malaise and listlessness). Reactions reported infrequently include mental confusion, anxiety, syncope, drowsiness, convulsions, coma, peripheral neuropathy, muscle weakness, involuntary muscle movements, insomnia, psychic disturbances such as depersonalisation, psychotic episodes and rarely, paresthesia, dysarthria, aggravation of epilepsy and parkinsonism. These often are transient and disappear frequently with continued treatment or with a reduction of dosage. However, the severity of these may, on occasion, require stopping therapy.

Gastrointestinal

Gastrointestinal reactions which occur most frequently are nausea, anorexia, vomiting, epigastric distress, abdominal pain, constipation, and diarrhoea. Others which may develop are ulceration – single or multiple – of oesophagus, stomach, duodenum or small or large intestine, including perforation and haemorrhage with a few fatalities having been reported; gastrointestinal tract bleeding without obvious ulcer formation; and increased abdominal pain when used in patients with preexisting ulcerative colitis. Rarely, intestinal ulceration followed by stenosis and obstruction has been reported. Reactions which occur infrequently are stomatitis; gastritis; flatulence; bleeding from the sigmoid colon – occult or from a diverticulum; and perforation of preexisting sigmoid lesions (diverticula, carcinoma). Other gastrointestinal side effects which may or may not be caused by INDOMETHACIN include ulcerative colitis and regional ileitis. Studies in humans with radioactive chromate tagged red blood cells indicate that the highest recommended oral dosage of INDOMETHACIN (50 mg, 4 times a day) produces less faecal blood loss than average doses of acetylsalicylic acid (600 mg, 4 times a day).

In a gastroscopic study in 45 healthy subjects, the number of gastric mucosal abnormalities was significantly higher in the group which received Capsules INDOMETHACIN than in the group taking Suppositories INDOMETHACIN or placebo.

In a double-blind comparative clinical study involving 175 patients with rheumatoid arthritis, however, the incidence of upper gastrointestinal adverse effects with Suppositories or Capsules INDOMETHACIN was comparable. The incidence of lower gastrointestinal adverse effects was greater in the suppository group.

Hepatic

Hepatic reactions reported on rare occasions in conjunction with INDOMETHACIN therapy are jaundice and hepatitis and some fatal cases have been reported.

Cardiovascular–Renal

Cardiovascular – renal reactions which may occur infrequently in conjunction with INDOMETHACIN therapy include oedema, elevation of blood pressure, tachycardia, chest pain, arrhythmia, palpitations, hypotension, congestive heart failure, BUN elevation, and haematuria.

Hypersensitivity

Hypersensitivity reactions reported infrequently are pruritus, urticaria, angitis, erythema nodosum, skin rashes, exfoliative dermatitis, Stevens-Johnson syndrome, erythema multiforme, toxic epidermal necrolysis, loss of hair, acute respiratory distress, a rapid fall in blood pressure resembling a shock-like state, acute anaphylaxis, angioneurotic oedema, sudden dyspnoea, asthma and pulmonary oedema.

Haematologic

Haematologic reactions which may develop infrequently in conjunction with INDOMETHACIN therapy are leucopenia, petechiae or ecchymosis, purpura, aplastic and haemolytic anaemia and thrombocytopenia, and disseminated intravascular coagulation. Rarely, agranulocytosis and bone marrow depression have been reported, but a definite relationship to INDOMETHACIN has not been

established. Some patients may manifest anaemia secondary to obvious or occult gastrointestinal bleeding. Therefore, appropriate blood determinations are recommended.

Eye

Blurred vision, diplopia and orbital and periorbital pain may occur infrequently. Corneal deposits and retinal disturbances, including those of the macula, have been reported in some patients with rheumatoid arthritis on prolonged therapy with INDOMETHACIN. Similar eye changes have been observed in some patients with this disease who have not received INDOMETHACIN.

Ear

Tinnitus, hearing disturbances, and deafness rarely, have been reported to occur.

Genitourinary

Reported rarely: proteinuria, nephrotic syndrome, interstitial nephritis and renal insufficiency, including renal failure.

Miscellaneous

Miscellaneous adverse reactions reported rarely in conjunction with INDOMETHACIN therapy include vaginal bleeding, hyperglycaemia and glycosuria, hyperkalemia, flushing and sweating, epistaxis, ulcerative stomatitis, and breast changes, including enlargement and tenderness, or gynecomastia.

Interactions

Acetylsalicylic Acid

The use of INDOMETHACIN in conjunction with acetylsalicylic acid or other salicylates is not recommended. Controlled clinical studies have shown that the combined use of INDOMETHACIN and acetylsalicylic acid does not produce any greater therapeutic effect than the use of INDOMETHACIN alone. Furthermore, in one of these clinical studies, the incidence of gastrointestinal side effects was significantly increased with combined therapy. In a study in normal volunteers, it was found that chronic concurrent administration of 3.6 g of acetylsalicylic acid per day decreases INDOMETHACIN blood levels approximately 20%.

Diflunisal

The combined use of INDOMETHACIN and diflunisal has been associated with fatal gastrointestinal haemorrhage. The co-administration of diflunisal and INDOMETHACIN results in an increase of about 30 – 35% in INDOMETHACIN plasma levels and a concomitant decrease in renal clearance of INDOMETHACIN and its conjugate. Therefore, INDOMETHACIN and diflunisal should not be used concomitantly.

Anticoagulants

Clinical studies have shown that INDOMETHACIN did not influence the hypoprothrombinaemia produced by anticoagulants in patients and in normal subjects. However, when any additional medicine, including INDOMETHACIN, is added to the treatment of patients on anticoagulant therapy, the patient should be observed closely for alterations of the prothrombin time.

Probenecid

When INDOMETHACIN is given to patients receiving probenecid, the plasma levels of INDOMETHACIN are likely to be increased. Therefore, a lower total daily dosage of INDOMETHACIN may produce a satisfactory therapeutic effect. When increases in the dose of INDOMETHACIN are made under these circumstances they should be made cautiously and in small increments.

Methotrexate

Caution should be used if INDOMETHACIN is administered simultaneously with methotrexate. INDOMETHACIN has been reported to decrease the tubular secretion of methotrexate and to potentiate toxicity.

Cyclosporin

Administration of non-steroidal anti-inflammatory medicines concomitantly with cyclosporin has been associated with an increase in cyclosporin-induced toxicity, possibly due to decreased synthesis of renal prostacyclin. NSAIDs should be used with caution in patients taking cyclosporin, and renal function should be monitored carefully.

Lithium

INDOMETHACIN 50 mg t.i.d. produced a clinically relevant elevation of plasma lithium and reduction in renal lithium clearance in psychiatric patients and normal subjects with steady state plasma lithium concentrations. This effect has been attributed to inhibition of prostaglandin synthesis. As a consequence, when INDOMETHACIN and lithium are given concomitantly, the patient should be observed carefully for signs of lithium toxicity. (Read circulars for lithium preparations before use of such concomitant therapy). In addition, the frequency of monitoring serum lithium concentrations should be increased at the outset of such combination medicine treatment.

Diuretics

In some patients, the administration of INDOMETHACIN can reduce the diuretic, natriuretic, and antihypertensive effects of loop, potassium-sparing, and thiazide diuretics. Therefore, when INDOMETHACIN and diuretics are used concomitantly, the patient should be observed closely to determine if the desired effect of the diuretic is obtained. INDOMETHACIN reduces basal plasma renin activity, (PRA) as well as those elevations of PRA induced by furosemide administration, or salt or volume depletion. These facts should be considered when evaluating plasma renin activity in hypertensive patients.

It has been reported that the addition of triamterene to a maintenance schedule of INDOMETHACIN resulted in reversible acute renal failure in two of four healthy volunteers. INDOMETHACIN and triamterene should not be administered together.

INDOMETHACIN and potassium-sparing diuretics each may be associated with increased serum potassium levels. The potential effects of INDOMETHACIN and potassium-sparing diuretics on potassium kinetics and renal function should be considered when these agents are administered concurrently.

Most of the above effects concerning diuretics have been attributed, at least in part, to mechanisms involving inhibition of prostaglandin synthesis by INDOMETHACIN.

Digoxin

INDOMETHACIN given concomitantly with digoxin has been reported to increase the serum concentration and prolong the half-life of digoxin. Therefore, when INDOMETHACIN and digoxin are used concomitantly, serum digoxin levels should be closely monitored.

Antihypertensive Medications

Co-administration of INDOMETHACIN and some antihypertensive agents has resulted in an attenuation of the latter's hypotensive effect acutely, due at least in part to INDOMETHACIN's inhibition of prostaglandin synthesis. The prescriber should, therefore, exercise caution when considering the addition of INDOMETHACIN to the regimen of a patient taking one of the following antihypertensive agents: an alpha-adrenergic blocking agent (such as prazosin), an angiotensin converting enzyme inhibitor (such as captopril or lisinopril), a beta-adrenergic blocking agent, a diuretic (see Diuretics), or hydralazine.

Phenylpropanolamine

Hypertensive crises have been reported due to oral phenylpropanolamine alone and rarely to phenylpropanolamine given with INDOMETHACIN. This additive effect is probably due at least in part to INDOMETHACIN's inhibition of prostaglandin synthesis. Caution should be exercised when INDOMETHACIN and phenylpropanolamine are administered concomitantly.

Overdosage

The following symptoms may be observed following overdosage: nausea, vomiting, intense headache, dizziness, mental confusion, disorientation, or lethargy. There have been reports of paresthesias, numbness, and convulsions.

Treatment is symptomatic and supportive. The stomach should be emptied as quickly as possible if the ingestion is recent. If vomiting has not occurred spontaneously, the patient should be induced to vomit with syrup of ipecac. If the patient is unable to vomit, gastric lavage should be performed. Once the stomach has been emptied, 25 or 50 g of activated charcoal may be given. Depending on the condition of the patient, close medical observation and nursing care may be required. The patient should be followed for several days because gastrointestinal ulceration and haemorrhage have been reported as adverse reactions of INDOMETHACIN. Use of antacids may be helpful.

Pharmaceutical Precautions

RHEUMACIN 25 mg and 50mg: Store below 30°C.

RHEUMACIN-SR 75 mg: Store below 25°C.

Medicine Classification

Prescription Medicine.

Package Quantities

RHEUMACIN-SR 75 mg (sustained release capsules) available in bottles of 100.

RHEUMACIN 25 mg capsules available in bottles of 100's & 250's.

RHEUMACIN 50 mg capsules available in bottles of 100's & 250's.

Further Information

Both RHEUMACIN 25mg and 50mg capsules contain lactose monohydrate, sodium starch glycollate, sodium lauryl sulfate, magnesium stearate and titanium dioxide.

Each RHEUMACIN 75mg SR capsule contains lactose monohydrate, povidone, purified talc, magnesium stearate, sucrose, maize starch and methacrylic acid copolymer.

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