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CLINICAL PHARMACOLOGY OF INDOMETHACIN

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ABSTRACT

Indomethacin is a methylated indole derivative indicated for the treatment of moderate-to-severe rheumatoid arthritis, osteoarthritis, ankylosing spondylitis, acute gouty arthritis, and acute painful shoulder. Indomethacin is a potent nonselective inhibitor of cyclooxygenase, inhibits the motility of polymorphonuclear leukocytes, and depresses the biosynthesis of mucopolysaccharides. Indomethacin, administered intravenously at the dose of 0.1 to 0.25 mg/kg twice-daily for three doses, is used to close the patent ductus arteriosus in preterm neonates and in adults the intravenous dose of indomethacin is 100 mg twice-daily or thrice-daily. Indomethacin has an excellent bioavailability. The efficacy and safely, the prophylaxis, and the treatment with indomethacin, and the trials conducted with indomethacin have been reviewed. Indomethacin is O-demethylated by CYP2C9, CYP1A2, and by CYP2D6 and is conjugated with glucuronic acid by UGT1A1, UGT1A3, UGT1A9, and by UGT2B7. Indomethacin is an active metabolite of acemetacin. The pharmacokinetics of indomethacin have been studied in health volunteers following the administration of a single dose and multiple doses of 90 mg of acemetacin sustained-release tablets and acemetacin sustained-release capsules. The elimination half-life of indomethacin is about 10 hours following the administration of single and multiple doses of both acemetacin formulations. The interaction of indomethacin with drugs and the toxicity induced by indomethacin have been reviewed. The aim of this study is to review the efficacy and safely, the prophylaxis, and the treatment with indomethacin. In addition, the trials conducted with indomethacin, the metabolism, and the pharmacokinetics of indomethacin, the interaction of indomethacin with drugs, and the toxicity induced by indomethacin have been reviewed.

KEYWORDS: Drug-interaction, effectively-safely, indomethacin, metabolism, pharmacokinetics, prophylaxis, toxicity, treatment, and trials.

INTRODUCTION

Indomethacin is a methylated indole derivative indicated for the treatment of moderate-to-severe rheumatoid arthritis, osteoarthritis, ankylosing spondylitis, acute gouty arthritis, and acute painful shoulder. Although indomethacin is still used clinically, mainly as a steroid-sparing agent, toxicity and the availability of safer alternatives have limited its use. Indomethacin is a potent nonselective inhibitor of the cyclooxygenase. It also inhibits the motility of polymorphonuclear leukocytes, depresses the biosynthesis of mucopolysaccharides, and may have a direct cyclooxygenase-independent vasoconstrictor effect. Indomethacin has prominent anti-inflammatory and analgesic-antipyretic properties like those of the salicylates.[1]

Therapeutic uses of indomethacin

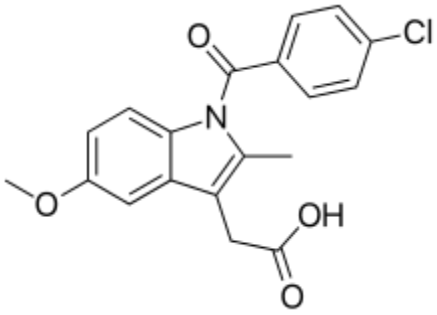
While indomethacin is estimated to be about 20-times more potent than aspirin, a high rate of intolerance limits its use. An intravenous formulation of indomethacin is approved for the closure of the patent ductus arteriosus in preterm neonates. The regimen involves intravenous administration of 0.1 to 0.25 mg/kg twice-daily for three doses, with the course repeated one-time if necessary. Successful closure can be expected in more than 70% of neonates treated. The principal limitation of treating neonates is a renal toxicity and therapy is interrupted if the output of urine falls significantly (< 0.6 ml/kg/h).[1]

Absorption, distribution, metabolism, and elimination of indomethacin

Oral indomethacin has excellent bioavailability. Peak concentrations occur 1 to 2 hours after dosing, is bound to plasma protein for 99%, is O-demethylated and glucuronidated, and is eliminated unchanged in the urine for 20%. The concentration in the cerebrospinal fluid is low, but its concentration in synovial fluid is equal to that in plasma within 5 hours of administration. There is enterohepatic cycling of the indomethacin metabolites and probably of indomethacin itself. The elimination half-life of indomethacin in plasma is variable, perhaps because of enterohepatic cycling, but averages to about 10 hours.[1]

Adverse-effects caused by indomethacin

A high percentage (35% to 50%) of patients receiving indomethacin experience adverse-effects. Gastrointestinal adverse-effects are common and can be fatal; elderly patients are at significant greater risk. Diarrhoea may occur and sometimes is associated with ulcerative lesions of the bowel. Acute pancreatitis has been reported, as have rare but potentially fatal, cases of hepatitis. Dizziness, vertigo, light-headedness, and mental confusion may occur. Seizures have been reported, as have severe depression, psychosis, hallucinations, and suicide. Caution is advised administrating indomethacin to elderly patients or to those with underlying epilepsy, psychiatric disorders, or Parkinson's disease because they are at greater risk for development of serious central nervous system adverse-effects. Hematopoietic reactions, including neutropenia, thrombocytopenia, and aplastic anaemia may occur. Concurrent administration of probenecid increases the total plasma concentration of indomethacin and its inactive metabolites. Indomethacin antagonizes the natriuretic and antihypertensive effects of β-receptor antagonists, AT_i receptor antagonists, and angiotensin-converting enzyme inhibitors.[1]



Indomethacin molecular structure (molecular weight = 357.79 grams/mole)

Literature search

The literature search was performed electronically using PubMed database as search engine and the following key words were used: "indomethacin efficacy, safely", "indomethacin prophylaxis", "indomethacin treatment", "indomethacin trials", "indomethacin metabolism", "indomethacin pharmacokinetics", "indomethacin drug-interaction", and "indomethacin toxicity". In addition the book: Goodman@Gilman's. The Pharmacological basis of Therapeutics[1] has been consulted.

RESULTS

Efficacy and safely of indomethacin

Three-hundred preterm neonates with hemodynamically significant patent ductus arteriosus were enrolled and randomized received either paracetamol intravenously at the dose of 15 mg/kg 4 times-daily for three days, or ibuprofen intravenously at the dose of 10 mg/kg followed by 5 mg/kg daily for two consecutive days, or indomethacin intravenously at the dose of 0.2 mg/kg twice-daily for three doses. Paracetamol is effective as ibuprofen and indomethacin for the closure of the patent ductus arteriosus and has fewer adverse-effects mainly on renal function, platelet count, and gastrointestinal bleeding.[2] One-hundred-forty-eight neonates with a gestational age of 24 to 32 weeks and with patent ductus arteriosus received either indomethacin intravenously at the dose of 0.2 mg/kg twice-daily for three doses or ibuprofen intravenously at the dose of 10 mg/kg followed by 5 mg/kg twice-daily for two doses and treatments started on the third day of life. The rate of ductal closure was similar in both treatments: ductal closure occurred in 49 of 74 neonates who received indomethacin (66.2%), and in 52 of 74 neonates who received given ibuprofen (70.3%) (P-value = 0.41). Oliguria occurred in 5 neonates treated with ibuprofen and in 14 treated with indomethacin (P-value = 0.03). Indomethacin is efficacious as ibuprofen for the closure of the patent ductus arteriosus and ibuprofen induces less oliguria.[3] Aceclofenac was administered at the dose of 100 mg twice-daily to 109 patients with rheumatoid arthritis and indomethacin was administered at the dose of 50 mg twice-daily to 100 patients with rheumatoid arthritis. The efficacy of aceclofenac was comparable to that of indomethacin. Among the 109 patients who received aceclofenac 26 patients (23.8%) had adverse-effects and 32 adverse-effects occurred in 100 patients (32.0%) who received indomethacin. Aceclofenac was effective as indomethacin in treatment of patients with rheumatoid arthritis and both drugs are well-tolerated.[4] Indomethacin was administered at the daily dose of 84 ± 32 mg to 26 patients with hemicrania continuous or with chronic paroxysmal hemicrania and the relief of symptoms occurred within 3 days of treatment. Six patients (23.1%) showed adverse-effects mostly gastrointestinal and no major adverse-effects were observed. These results indicate that treatment with indomethacin effectively and safely treated patients with hemicrania continuous or chronic paroxysmal hemicranias.[5]

Prophylaxis with indomethacin

A total of 1,202 neonates with birth-weight of 500 to 999 grams were enrolled. Five-hundred-seventy-four neonates (47.7%) received indomethacin intravenously at the daily dose of 0.1 mg/kg for three consecutive days and 628 neonates (52.2%) received placebo. Indomethacin reduced the incidence of patent ductus arteriosus in 24.1% of neonates and placebo reduced the incidence of patent ductus arteriosus in 50.0% of

neonates (P-value < 0.001). Severe periventricular and intraventricular haemorrhage occurred in 9.2% of neonates who received indomethacin and in 13.1% of neonates who received placebo (P-value < 0.02). Prophylactic indomethacin is more effective than placebo for the closure of the patent ductus arteriosus and in preventing periventricular and intraventricular haemorrhage in extremely-low-birth-weight neonates.[6] A total of 4,760 neonates with a median gestational age of 24.6 weeks and with a median birth-weight of 640 grams were enrolled. Neonates had amniotic infection syndrome and intraventricular haemorrhage and received indomethacin intravenously at the daily dose of 0.1 mg/kg for three consecutive days. Indomethacin treated amniotic infection syndrome and prevented the intraventricular haemorrhage in neonates.[7] Patients with heterotopic ossification received either indomethacin at the daily dose of 100 mg, or ibuprofen at the daily dose of 100 mg, or placebo and treatments lasted three weeks. Indomethacin and ibuprofen demonstrated similar efficacy in preventing heterotopic ossification and both indomethacin and ibuprofen were more effective than placebo in preventing heterotopic ossification.[8] Two-hundred-forty-one patients with acute pancreatitis received either gabexate mesylate intravenously at the daily dose of 100 mg or indomethacin rectally at the daily dose of 100 mg. Prophylaxis with indomethacin is better (P-value < 0.05) than that with gabexate mesylate in treatment of patients with acute pancreatitis.[9] Three-hundred-sixty-seven patients with acute pancreatitis received either indomethacin rectally at the daily dose of 100 mg or placebo. Rectal indomethacin was more effective (P-value < 0.05) than placebo in treating patients with acute pancreatitis.[10] Five-hundred patients with cystoid macular oedema received indomethacin topically or placebo for nine months after surgery. The incidence of cystoid macular oedema was significantly higher in patients who received placebo (18.5%) than in patients who received indomethacin (9.6%) (P-value = 0.04). Topical indomethacin prevents cystoid macular oedema more effectively than placebo.[11]

Treatment with indomethacin

Thirty-two preterm neonates with symptomatic patent ductus arteriosus received indomethacin intravenously at the daily dose of 0.1 mg/kg for one week and the closure of the patent ductus arteriosus was observed in 63.1% of neonates. Eighty-five percent of neonates, weighing more than 1,000 grams, were treated successfully and only four of these neonates (22.2%) experienced adverse-effects. The benefit-to-risk ratio was lowest in neonates weighing 1,000 grams or less (N = 12; 37.5%) with a success-rate of 25.0% and severe adverse-effects were observed in 10 neonates (31.2%). Prolonged treatment with indomethacin is an alternative to conventional short-term treatment and appears to be particularly efficacious and safe in neonates weighing more than 1,000 grams.[12] Twenty-three preterm neonates with patent ductus arteriosus received either indomethacin at the daily dose of 0.2 mg/kg for three consecutive days or placebo. In treatment group, 7 neonates out of a total of 12 (58.3%) responded to treatment while 2 of 11 neonates (18.2%) who received the placebo responded to treatment (P-value < 0.05). Indomethacin was more effective than placebo in closing the patent ductus arteriosus of preterm neonates.[13] Ninety-five preterm neonates with patent ductus arteriosus received either indomethacin intravenously at the daily dose of 0.1 mg/kg for six doses, or indomethacin at the daily dose of 0.2 mg/kg for three doses, or ibuprofen intravenously at the dose of 10, 5, and 5 mg/kg for three consecutive days. The failure-rate of treatment and the proportion of neonates having surgical ligation were similar in the three treatments. A higher rate of intestinal complications (necrotising enterocolitis or spontaneous intestinal perforation) was higher in neonates who received ibuprofen than in those who received indomethacin (P-value = 0.043). Indomethacin and ibuprofen were equally effective for the closure of patent ductus arteriosus in preterm neonates and indomethacin is better tolerated than ibuprofen.[14] Thirteen pregnant women in premature labour, with a gestational age of 26.5 to 31.0 weeks, received indomethacin intravenously at the daily dose of 100 to 175 mg for a maximum of 72 hours. The detection of ductal constriction was observed in 7 of 14 neonates (50.0%) who led to the discontinuation of indomethacin. In these neonates the ductal constriction resolved by 24 hours after the discontinuation of indomethacin treatment. Indomethacin used to treat women in premature labour appears to cause transient constriction of the ductus arteriosus in one-half of neonates.[15] Indomethacin was administered intravenously at the daily dose of 150 mg for the first week of treatment and at the daily 100 mg for two additional weeks to 18 patients with Sweet's syndrome. The therapeutic response was assessed on days 4, 7, 14, 30, and 180 of treatment. Seventeen of 18 patients (94.4%) had a good initial response and the only adverse-effect was epigastric pain which occurred in only two patients (11.1%). Indomethacin is a safe and effective treatment for Sweet's syndrome.[16] Five head-injured patients with cerebral contusion and cerebral oedema received indomethacin intravenously at the dose of 30 mg followed by 30 mg hourly for seven hours and the reduction of intracranial pressure below 20 mm Hg was observed in all patients and indomethacin treatment was followed by a fall in rectal temperature. Indomethacin due to its cerebral vasoconstrictor and antipyretic effect should be considered as an alternative for treatment of intracranial hypertension in head-injured patients.[17] Indomethacin was administered intravenously at the dose of 30 mg followed by 30 mg hourly for seven hours to five patients with severe head-injury with resistant intracranial hypertension. All patients had focal cerebral contusion and cerebral oedema with compression of the ventricular system and basal cisterns. The intracranial pressure decreased from 27 to 17 mm Hg followed by a decrease of cerebral flow and an increase in the arteriovenous lactate difference. Indomethacin decreased

the intracranial hypertension in patients with severe head-injury but the cerebral vasoconstrictor effect of indomethacin was potentially dangerous because it might provoke cerebral ischemia.[18] Of 149 patients with osteoarthritis of the hip, 79 patients (53.0%) received indomethacin intravenously at the daily dose of 100 mg and 71 patients (47.6%) did not received indomethacin. In treated patients the disease progressed more frequently than in untreated patients.[19] Patients with acute gout received either lumiracoxib intravenously at the dose of 400 mg once-daily (N = 118) or received indomethacin intravenously at the dose of 50 mg thrice-daily (N = 117). The primary efficacy endpoint was the mean change in pain intensity from baseline over days 2 to 5 of treatment. The estimated difference between treatments for the change from baseline in pain intensity showed that lumiracoxib had comparable efficacy to that of indomethacin. Adverse-effects were reported in 10.2% of patients treated with lumiracoxib and in 22.2% of those treated with indomethacin (P-value < 0.05). Lumiracoxib was effective as indomethacin for treatment of acute gout and has a better safely and tolerability.[20]

Trials conducted with indomethacin

A randomized, controlled trial was conducted in 175 preterm neonates, with a gestational age of 23 to 34 weeks and with respiratory distress syndrome, who had the patent ductus arteriosus at 48 to 72 hours of life. Neonates received either indomethacin intravenously at the dose of 0.2 mg/kg twice-daily for three consecutive days (N = 81; 46.2%) or ibuprofen intravenously at the dose of 10 mg/kg followed by two doses of 5 mg/kg (N = 94; 53.7%). The closure of the patent ductus arteriosus occurred in 59.1% of neonates who received indomethacin and in 73.4% in neonates who received ibuprofen. Neonates treated with indomethacin showed a significant increase in serum creatinine concentration (89±24 versus 82±20 mmol/L; P-value = 0.03) and a near-significant tendency for a lower fractional excretion of sodium (3±3% versus 4±2%; P-value = 0.08) than neonates treated with ibuprofen. Moreover, 14.8% of neonates who received indomethacin versus 1.0% of neonates who received ibuprofen became oliguric (< 1 ml/kg/h; P-value = 0.017). Ibuprofen and indomethacin closed the patent ductus arteriosus in similar percentage and ibuprofen was better tolerated than indomethacin.[21]

A randomized, prospective trial was conducted in 105 preterm neonates with a gestational age < 37 weeks and with patent ductus arteriosus. Neonates received either oral indomethacin at the initial dose of 0.2 mg/kg followed by two doses of 0.2 mg/kg, or oral ibuprofen at the initial dose of 10 mg/kg followed by two doses of 5 mg/kg, or intravenous paracetamol at the dose of 15 mg/kg 4 times-daily for three consecutive days. There was no significant difference in the closure of the patent ductus arteriosus among the three treatments. The closure of the patent ductus arteriosus occurred in 68.1% in neonates treated with indomethacin, in 77.1% of neonates treated with ibuprofen, and in 71.4% in neonates treated with paracetamol (P-value = 0.716). There was no significant change in haemoglobin concentration, in platelet number, in blood urea nitrogen concentration, in serum creatinine concentration, and in liver enzymes after the treatment with paracetamol. Blood urea nitrogen and serum creatinine concentrations were significantly increased after treatment with indomethacin and ibuprofen (P-value < 0.0001 and P-value < 0.05, respectively). Intravenous paracetamol is as effective as oral indomethacin and as oral ibuprofen for the closure of the patent ductus arteriosus and paracetamol had a better safely profile.[22] A multicentre, randomized, placebo-controlled, double-blind, clinical trial was conducted in 602 patients with elevated risk for post-endoscopic pancreatitis who received either a single dose of 100 mg of rectal indomethacin or placebo. Post-endoscopic pancreatitis developed in 27 of 295 patients (9.2%) who received indomethacin and in 52 of 307 patients (16.9%) who received placebo (P-value = 0.005). Moderate-to-severe post-endoscopic pancreatitis developed in 13 patients (4.4%) who received indomethacin group and in 27 patients (8.8%) who received placebo (P-value = 0.03). Rectal indomethacin reduced the incidence of post-endoscopic pancreatitis more effectively than placebo.[23] A double-blind, crossover trial compared the efficacy and tolerability of controlled-release indomethacin tablets to those of sustained-release diclofenac sodium tablets in patients with osteoarthritis. Eighty-four patients received either controlled-release indomethacin tablets at the daily dose of 75 mg (N = 51; 60.7%) and 33 patients (39.3%) received sustained-release diclofenac sodium tablets at the daily dose of 100 mg daily at night for four weeks. Pain scores for day and night, duration of morning stiffness, requirement for escape analgesia, and treatment preference were similar with both drugs. There was no significant difference between treatments in the incidence of adverse-effects. Controlled-release indomethacin tablets were efficacious and well-tolerated as sustained-release diclofenac sodium tablets.[24]

Metabolism of indomethacin

Nakajima et al.[25] observed that indomethacin is O-demethylated in human liver microsomes and the O-demethylation of indomethacin is a major metabolic pathway of indomethacin metabolism. The K_m and the V_{max} values of O-demethylation of indomethacin were 34.6±5.4 µM and 14.1±3.9 pmol/mg/min, respectively. The cytochromes P-450 that catalyse the O-demethylation of indomethacin are CYP2C9, CYP1A2, and CYP2D6. Mano et al.[26] studied the glucuronidation of indomethacin in human liver microsomes and observed that indomethacin is glucuronidated by UGT1A1, UGTIA3, UGT1A9, and by UGT2B7 and propofol inhibited the glucuronidation of indomethacin in human liver microsomes with an IC_{50} value of 248 µM.

Pharmacokinetics of indomethacin

Li et al.[27] studied the pharmacokinetics of indomethacin, an active metabolite of acemetacin, in 10

male health volunteers, aged 20 to 30 years, and with body weight of 53 to 75 kg. Five volunteers received a single oral dose of 90 mg of acemetacin administered as sustained-release tablets or as sustained-release capsules and five volunteers received multiple oral doses of 90 mg once-daily of acemetacin administered as sustained-release tablets or administered as sustained-release capsules. Table 1 shows the pharmacokinetic parameters of indomethacin obtained following a single oral dose of 90 mg of acemetacin administered as sustained-release tablets or as sustained-release capsules and table 2 shows the pharmacokinetic parameters of indomethacin obtained following multiple oral doses of 90 mg once-daily of acemetacin administered as sustained-release tablets or as sustained-release capsules.

Table 1: Pharmacokinetic parameters of indomethacin which have been obtained following a single oral dose of 90 mg of acemetacin administered as sustained-release tablets or as sustained-release capsules. Values are the mean±SD, by Li et al.[27]

Parameter	Sustained-release tablets	Sustained-release capsules
$AUC_{0\text{-}24\ h}$ (µg*h/ml)	6.72±0.99	7.11±0.50
$AUC_{0\text{-}\infty}$ (µg*h/ml)	8.56±0.95	8.73±0.91
Peak concentration (µg/ml)	0.82±0.08	0.97±0.07
Time to reach the peak concentration (h)	4.2±0.6*	3.2±0.6
Elimination half-life (h)	10.1±4.2	9.6±3.4
Mean residence time (h)	15.5±3.5	13.4±3.6

AUC = area under the concentration-time curve. *P-value < 0.05 (Student t test for unpaired data). This table shows that indomethacin is slowly eliminated as the elimination half-life of indomethacin is about 10 hours and the mean residence time of indomethacin is longer than the elimination half-life of indomethacin. The only parameter that varies according to the two formulations of acemetacin is the time to reach the peak concentration of indomethacin which is longer in volunteers who received acemetacin administered as sustained-release tablets than in volunteers who received acemetacin administered as sustained-release capsules.

Table 2: Pharmacokinetic parameters of indomethacin which have been obtained following multiple oral doses of 90 mg once-daily of acemetacin administered as sustained-release tablets or as sustained-release capsules. Values are the mean±SD, by Li et al.[27]

Parameter	Sustained-release tablets	Sustained-release capsules
$AUC_{120\text{-}144\ h}$ (µg*h/ml)	10.33±1.06	10.65±1.12
$AUC_{120h\text{-}\infty}$ (µg*h/ml)	12.86±1.56	13.19±1.66
Peak concentration at the steady-state (µg/ml)	1.14±0.10	1.18±0.08
Trough concentration at the steady-state (µg/ml)	0.17±0.03	0.16±0.02
Mean concentration at the steady-state (µg/ml)	0.43±1.21	0.42±1.1
Time to reach the peak concentration (h)	4.1±0.7*	3.4±0.5
Elimination half-life (h)	9.3±1.9	9.3±1.9
Mean residence time (h)	14.5±1.17	14.2±1.9

AUC = area under the concertation-time curve. *P-value < 0.05 (Student t test for unpaired data).

This table shows that the elimination half-life of indomethacin, obtained following the administration of multiple doses of acemetacin, is similar to that obtained following the administration of a single dose of acemetacin (see table 1) indicating that indomethacin does not accumulate in plasma and the mean residence time of indomethacin is longer than the elimination half-life of indomethacin. The only parameter that varies according to the two formulations of acemetacin is the time to reach the peak concentration which is longer in volunteers who received acemetacin administered as sustained-release tablets than in volunteers who received acemetacin administered as sustained-release capsules. In addition, there is a remarkable interindividual variability in the pharmacokinetic parameters of indomethacin. In particular, the standard deviation is greater than the mean of the mean concentration of indomethacin at the steady-state. This variability is accounted by the wide variation of the vital data of subjects included in the study.

Interaction of indomethacin with drugs

Diflunisal, administered at the daily dose of 250 mg, inhibited the glucuronidation of indomethacin with an IC_{50} values ranging from 100 to 231 µM.[28] Indomethacin was administered at the daily dose of 300 mg and acetylsalicylic acid was administered at the daily dose of 2,000 to 3,000 mg to 8 patients and acetylsalicylic acid induced the metabolism of indomethacin.[29] Concomitant intake of indomethacin and sulfasalazine increased the absorption of sulfasalazine in the small intestine reducing the colonic concentration of sulfasalazine and altering its therapeutic effect.[30] Indomethacin, administered at the dose of 50 mg thrice-daily, increased the serum concertation of digoxin to values higher the therapeutic range.[31]

Toxicity induced by indomethacin

Indomethacin is associated with more severe renal adverse-effects than ibuprofen in preterm neonates and ibuprofen should be used to close the patent ductus arteriosus.[32] Indomethacin caused necrotizing enterocolitis in preterm neonates in the first 15 days of life.[33] A 71-year-old woman, with no previous mental health history, received indomethacin at the daily dose of 150 mg and indomethacin caused psychosis.[34] A 53-year-old woman received indomethacin at the daily dose ranging from 50 to 200 mg and this treatment caused psychosis.[35] Thirty-two parturients received indomethacin at the daily dose of 100 mg and the patients experienced psychiatric reactions. The symptoms were often severe and included dizziness, anxiety, fear, agitation, affective lability, depersonalization, paranoia, and hallucinations.[36] The ocular adverse-effects were observed in 32 patients who received 1% topical indomethacin eye drops for treatment of chronic cystoid macular oedema.[37] Corneal complications are associated with the administration of 1% topical indomethacin.[38] A 73-year-old woman, with a 13-year history of rheumatoid arthritis, was treated for corneal ulceration with 1% topical indomethacin and the main lesions were the inflammation of the anterior segment of the eye.[39]

DISCUSSION

Indomethacin is a methylated indole derivative indicated for the treatment of moderate-to-severe rheumatoid arthritis, osteoarthritis, ankylosing spondylitis, acute gouty arthritis, and acute painful shoulder. Indomethacin is a potent nonselective inhibitor of the cyclooxygenase and inhibits the motility of polymorphonuclear leukocytes, depresses the biosynthesis of mucopolysaccharides, and may have a direct cyclooxygenase-independent vasoconstrictor effect. Indomethacin, administered intravenously at the dose of 0.1 to 0.25 mg/kg twice-daily for three doses, is used to close the patent ductus arteriosus in preterm neonates and in adults the intravenous dose of indomethacin is 100 mg twice-daily or thrice-daily. Oral indomethacin has excellent bioavailability, the peak concentrations of indomethacin occur 1 to 2 hours after dosing, indomethacin is bound to plasma protein for 99%, and there is an enterohepatic cycling of indomethacin and its metabolises. About 35% to 50% of patients receiving indomethacin experience adverse-effects. Gastrointestinal adverse-effects are common, diarrhoea may occur and may be associated with ulcerative lesions of the bowel, acute pancreatitis has been reported, and dizziness, vertigo, light-headedness, confusion, seizures, severe depression, psychosis, hallucinations, and suicide may occur. Indomethacin should be administered with caution to elderly patients and to those with epilepsy, psychiatric disorders, and Parkinson's disease because they are at greater risk for development of serious central nervous system adverse-effects.[1] The efficacy and safely of indomethacin have been reviewed. Preterm neonates with patent ductus arteriosus received either paracetamol intravenously at the dose of 15 mg/kg 4 times-daily for three consecutive days, or ibuprofen intravenously at the dose of 10 mg/kg followed by 5 mg/kg for two consecutive days, or indomethacin intravenously at the dose of 0.2 mg/kg twice-daily for three doses. Paracetamol effectively closes the patent ductus arteriosus as ibuprofen and indomethacin and causes fewer adverse-effects such as renal function, platelet count, and gastrointestinal bleeding[2], neonates with patent ductus arteriosus received either indomethacin intravenously at the dose of 0.2 mg/kg twice-daily for three doses or ibuprofen intravenously at the dose of 10 mg/kg followed by 5 mg/kg twice-daily for two doses. Indomethacin is effective as ibuprofen for the closure of the patent ductus arteriosus and ibuprofen induces less oliguria[3], aceclofenac was administered at the dose of 100 mg twice-daily and indomethacin was administered at the dose of 50 mg twice-daily to patients with rheumatoid arthritis and aceclofenac is effective as indomethacin in treatment of patients with rheumatoid arthritis and both drugs are well-tolerated[4], indomethacin was administered at the daily dose of 84 ± 32 mg to patients with hemicrania or with chronic paroxysmal hemicrania and indomethacin effectively and safely treats the patients.[5] The prophylaxis with indomethacin has been reviewed. Extremely-low-birth-weight neonates with patent ductus arteriosus received either indomethacin intravenously at the daily dose of 0.1 mg/kg for three consecutive days or received placebo. Indomethacin closes the patent ductus arteriosus more effectively than placebo (P-value < 0.001) and prevents severe periventricular and intraventricular haemorrhage more effectively than placebo (P-value < 0.02)[6], neonates with amniotic infection syndrome and with intraventricular haemorrhage received indomethacin at the daily dose of 0.1 mg/kg for three consecutive days and indomethacin treats amniotic infection syndrome and prevents intraventricular haemorrhage[7], patients with heterotopic ossification received either indomethacin at the daily dose of 100 mg, or ibuprofen at the daily dose of 100 mg, or placebo and the treatments lasted three days. Indomethacin and ibuprofen are more effective than placebo in preventing heterotopic ossification[8], patients with acute pancreatitis received either gabexate mesylate intravenously at the daily dose of 100 mg or indomethacin rectally at the daily dose of 100 mg and indomethacin prevents acute pancreatitis better (P-value < 0.05) than gabexate mesylate[9], patients with acute pancreatitis received either indomethacin at the daily dose of 100 mg or placebo and indomethacin prevents acute pancreatitis better (P-value < 0.05) than placebo[10], and patients with cystoid macular oedema received either topical indomethacin or placebo and the incidence of cystoid macular oedema is higher (P-value = 0.04) in patients who received the placebo.[11] The treatment with indomethacin has been reviewed. Preterm neonates with patent ductus arteriosus received indomethacin intravenously at the daily dose of 0.1 mg/kg for one week and the closure of the patent ductus arteriosus occurs in 63.1% of neonates. Eighty-five percent of

neonates weighing more than 1,000 mg were treated successfully and only four of these neonates (22.2%) experience adverse-effects. The benefit-to-risk ratio is lowest in neonates weighing 1,000 grams or less, prolonged treatment with indomethacin is particularly efficacious and safe in neonates weighing more than 1,000 grams[12], preterm neonates with patent ductus arteriosus received indomethacin intravenously at the daily dose of 0.2 mg/kg for three consecutive days or placebo. The closure of the patent ductus arteriosus occurs in 58.3% of neonates who received indomethacin and 18.2% of neonates who received placebo (P-value < 0.05). Indomethacin is more effective than placebo in closing the patent ductus arteriosus[13], preterm neonates with patent ductus arteriosus received either indomethacin intravenously at the daily dose of 0.1 mg/kg for six doses, or indomethacin intravenously at the daily dose of 0.2 mg/kg for three doses, or ibuprofen intravenously at the daily dose of 10 mg/kg followed by 5 mg/kg for three consecutive days. The failure of treatment and the proportion of neonates having surgical ligation are similar with the three treatments. Indomethacin is better tolerated than ibuprofen and indomethacin and ibuprofen are equally effective for the closure of the patent ductus arteriosus[14], parturients received indomethacin at the dose of 100 to 175 mg for a maximum of 72 hours and the closure of patent ductus arteriosus occurs in one-half of neonates[15], indomethacin was administered intravenously at the daily dose of 150 mg during the first week of treatment and at the daily dose of 100 mg for two additional weeks to patients with Sweet's syndrome and this treatment treats 94.4% of patients and the adverse-effect such as the epigastric pain occurs in only 11.1% of patients[16], head-injured patients with cerebral contusion and cerebral oedema received indomethacin intravenously at the dose of 30 mg followed by 30 mg hourly for seven hours and the reduction of intracranial pressure below 20 mm Hg is observed in all patients and indomethacin causes a fall of rectal temperature. The cerebral vasoconstriction and the antipyretic effect of indomethacin makes indomethacin a treatment of intracranial hypertension in head-injured patients[17], indomethacin was administered intravenously at the dose of 30 mg followed by 30 mg hourly for seven hours to patients with severe head-injury. All patients had focal cerebral contusion and cerebral oedema with compression of the ventricular system and basal cistern. The intracranial pressure decreased from 27 to 10 mm Hg followed by a decrease of the cerebral flow and an increase in the arteriovenous lactate difference. Indomethacin decreases the intracranial hypertension but the cerebral vasoconstriction effect of indomethacin is potentially dangerous because it might provoke cerebral ischemia[18], patients with osteoarthritis (N = 79; 53.0%) received indomethacin intravenously at the daily dose of 100 mg and patients (N = 71; 47.6%) did not receive indomethacin. In treated patients the disease progresses more frequently than in untreated patients[19], and patients with gout received either lumiracoxib intravenously at the dose of 400 mg once-daily or indomethacin intravenously at the dose of 50 mg thrice-daily. Lumiracoxib is effective as indomethacin in treatment of patients with gout and the adverse-effects occur in 10.2% of patients who received lumiracoxib and in 22.2% (P-value < 0.05) in patients who received indomethacin.[20] The trials conducted with indomethacin have been reviewed. A randomized, controlled trial was conducted in preterm neonates with respiratory distress syndrome and with patent ductus arteriosus who received either indomethacin intravenously at the dose of 0.2 mg/kg twice-daily for three consecutive days or ibuprofen intravenously at the dose of 10 mg/kg followed by two doses of 5 mg/kg. The closure of the patent ductus arteriosus occurs in similar percentage in neonates who received indomethacin and in those who received ibuprofen and ibuprofen causes fewer adverse-effects on renal function in terms of urine output and fluid retention[21], a randomized, prospective trial was conducted in preterm neonates with patent ductus arteriosus who received either indomethacin orally at the initial dose of 0.2 mg/kg followed by two doses of 0.2 mg/kg, or ibuprofen orally at the initial dose of 10 mg/kg followed by two doses of 5 mg/kg, or paracetamol intravenously at the dose of 15 mg/kg 4 times-daily administered for three consecutive days. These treatments are similarly effective in closing the patent ductus arteriosus and are well-tolerated but blood urea nitrogen and serum creatinine concentrations significantly increased after treatment with indomethacin and with ibuprofen (P-value < 0.0001 and P-value < 0.05, respectively). Intravenous paracetamol, oral indomethacin, and oral ibuprofen are equally effective in closing the patent ductus arteriosus and paracetamol has a better safe profile[22], a multicentre, randomized, placebo-controlled, double-blind, clinical trial was conducted in patients with elevated risk for post-endoscopic pancreatitis who received either a single dose of 100 mg of rectal indomethacin or placebo. Post-endoscopic pancreatitis develops more frequently (P-value = 0.005) in patients who received placebo and moderate-to-severe pancreatitis occur more frequently (P-value = 0.03) in patients who received placebo. Rectal indomethacin reduces the incidence of post-endoscopic pancreatitis more effectively than placebo[23], and a double-blind, crossover trial compared the efficacy and tolerability of a controlled-release indomethacin tablets (75 mg daily) with sustained-release diclofenac sodium tablets (100 mg daily) in patients with osteoarthritis. Pain scores for day and night, duration of morning stiffness, requirement for escape analgesia, and treatment preference are similar with both treatments. Controlled-release indomethacin tablets are efficacious and well-tolerated as sustained-release diclofenac sodium tablets in controlling pain, in escaping analgesia, in and in reducing morning stiffness.[24] The metabolism of indomethacin has been reviewed. Indomethacin is O-demethylated in human liver microsomes and the O-demethylation of indomethacin is a major metabolic pathway of indomethacin. The cytochromes that catalyse

the O-demethylation of indomethacin are CYP2C9, CYP1A2, and CYP2D6[25] and indomethacin is glucuronidated in human liver microsomes and the glucuronidation of indomethacin is catalysed by UGT1A1, UGT1A3, UGT1A9, and by UGT2B7.[26] Li et al.[27] studied the pharmacokinetics of indomethacin, an active metabolite of acemetacin, in five male healthy volunteers who received a single oral dose of 90 mg of acemetacin administered as sustained-release tablets or as sustained-release capsules and in five healthy male volunteers who received multiple oral doses of 90 mg once-daily of acemetacin administered as sustained-release tablets or as sustained-release capsules. The elimination half-life of indomethacin is about 10 hours according to both formulations of acemetacin in volunteers who received a single dose and in volunteers who received multiple doses of both formulations of acemetacin indicating that indomethacin is slowly eliminated and does not accumulate in plasma. With the exception of the time to reach the peak concentration of indomethacin, all pharmacokinetic parameters of indomethacin are similar according to the two formulations of acemetacin. The time to reach the peak concentration of indomethacin is longer following the administration of sustained-release tablets than following the administration of sustained-release capsules in volunteers who received a single dose and multiple doses of both acemetacin formulations. The interaction of indomethacin with drugs has been reviewed. Diflunisal inhibits the glucuronidation of indomethacin[28], acetylsalicylic acid induces the metabolism of indomethacin[29], concomitant intake of indomethacin and sulfasalazine increases the absorption of sulfasalazine in the small intestine reducing the colonic concentration of sulfasalazine and altering its therapeutic effect[30], and indomethacin, administered at the dose of 50 mg thrice-daily, increases the serum concentration of digoxin to values higher the therapeutic range.[31] The toxicity induced by indomethacin has been reviewed. Indomethacin is associated with more severe renal adverse-effects than ibuprofen in preterm neonates and ibuprofen should be used to close the patent ductus arteriosus[32], indomethacin causes necrotizing enterocolitis in preterm neonates in the first 15 days of life[33], indomethacin, administered at the daily dose of 150 mg, causes psychosis in a woman[34], indomethacin, administered at the daily dose of 50 to 200 mg, causes psychosis in a woman[35], indomethacin, administered at the daily dose of 100 mg to parturients, causes psychiatric adverse-effects and the symptoms include dizziness, anxiety, fear, agitation, affective lability, depersonalization, paranoia, and hallucinations[36], ocular adverse-effects are observed in patients who received 1% topical indomethacin eye drops for treatment of chronic cystoid macular oedema[37], corneal complications are associated with the administration of 1% topical indomethacin[38], and a women was treated for corneal ulceration with 1% topical indomethacin and the main lesions were the inflammation of the anterior segment of the eye.[39]

In conclusion, indomethacin is a methylated indole derivative indicated for the treatment of moderate-to-severe rheumatoid arthritis, osteoarthritis, ankylosing spondylitis, acute gouty arthritis, and acute painful shoulder. Indomethacin is a potent nonselective inhibitor of the cyclooxygenase. An intravenous formulation of 0.1 to 0.25 mg/kg of indomethacin is available for the closure of the patent ductus arteriosus in preterm neonates and the intravenous dose of indomethacin in adults is 100 mg twice-daily or thrice-daily. The efficacy and safely, the prophylaxis, the treatment, and the trials conducted with indomethacin have been reviewed. Indomethacin is O-demethylated and is glucuronidated in human liver microsomes. The pharmacokinetics of indomethacin have been studied in healthy volunteers and the elimination half-life of indomethacin in about 10 hours. The interaction of indomethacin with drugs and the toxicity induced by indomethacin have been reviewed. The aim of this study is to review the clinical pharmacology of indomethacin.

CONFLICT OF INTERESTS

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This article is a review and drugs have not been administered to men or animals.

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