PRODUCT MONOGRAPH

Indocid® P.D.A.
(indomethacin sodium for injection)

LYOPHILIZED

Equivalent to 1 mg indomethacin/vial

INTRAVENOUS USE ONLY

THERAPEUTIC CLASSIFICATION
Non-steroidal anti-inflammatory agent for closure of Patent Ductus Arteriosus

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Date of Revision:
January 26, 2010

Control #: 133722

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CLINICAL PHARMACOLOGY

INDOCID P.D.A. (indomethacin sodium for injection) is a non-steroidal anti-inflammatory agent which inhibits prostaglandin synthesis. The disposition of indomethacin following intravenous administration (0.2 mg/kg) in preterm infants with patent ductus arteriosus has not been extensively evaluated. Even though the plasma half-life of indomethacin was variable among premature infants, it was shown to vary inversely with postnatal age and weight. In one study of 28 evaluable neonates, the plasma half-life in those neonates less than 7 days old averaged 20 hours (range: 3-60 hours, n=18). In neonates older than 7 days, the mean plasma half-life of indomethacin was 12 hours (range 4-38 hours, n=10). Grouping the neonates by weight, mean plasma half-life in those weighing less than 1000 g was 21 hours (range: 9-60 hours, n=10); in those neonates weighing more than 1000 g, the mean plasma half-life was 15 hours (range: 3-52 hours, n=18).

Following intravenous administration in adults, 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. Indomethacin exists in the plasma as the parent drug and its desmethyl, desbenzoyl, and desmethyl-desbenzoyl metabolites, all in the unconjugated form. About 60 percent of an oral dosage is recovered in urine as drug and metabolites (32 percent as indomethacin and its glucuronide), and 33 percent is

recovered in feces (1 percent as indomethacin). About 99 percent of indomethacin is bound to protein in plasma over the expected range of therapeutic plasma concentrations.

The percent bound in neonates has not been studied. In controlled trials in premature infants, however, no evidence of bilirubin displacement has been observed as evidenced by increased incidence of bilirubin encephalopathy (kernicterus).

INDICATION AND CLINICAL USE

INDOCID P.D.A. (indomethacin sodium for injection) has been used to close hemodynamically significant patent ductus arteriosus in premature infants weighing between 500 and 1750 g when after 48 hours usual medical management (e.g., fluid restriction, diuretics, digitalis, respiratory support) is ineffective. Clearcut clinical evidence of a hemodynamically significant patent ductus arteriosus should be present, such as respiratory distress, a continuous murmur, a hyperactive precordium, cardiomegaly and pulmonary plethora on chest x-ray.

INDOCID P.D.A. is indicated to close a patent ductus arteriosus in premature infants when usual medical management is ineffective.

CONTRAINDICATIONS

INDOCID P.D.A. (indomethacin sodium for injection) is contraindicated in:

- neonates with proven or suspected infection that is untreated;
- neonates who are bleeding, especially those with active intracranial hemorrhage or gastrointestinal bleeding;
- in neonates with congenital heart disease in whom patency of the ductus arteriosus is necessary for satisfactory pulmonary or systemic blood flow (e.g., pulmonary atresia, severe tetralogy of Fallot, severe coarctation of the aorta);
- neonates with thrombocytopenia;
- neonates with coagulation defects;
- neonates with or who are suspected of having necrotizing enterocolitis;
- neonates with significant impairment of renal function;
- jaundiced infants with bilirubin ≥10 mg/dL (≥171 µmol/L) or those with known hepatic diseases.

WARNINGS

Renal Effects

INDOCID P.D.A. (indomethacin sodium for injection) may cause significant reduction in urine output (50% or more) with concomitant elevations of blood urea nitrogen and creatinine (greater than or equal to 1.8 mg/dL [≥159 µmol/L]), and reductions in glomerular filtration rate and creatinine clearance (see ADVERSE REACTIONS). Most of the renal abnormalities reported have been reversible but some fatalities occurred. However, because adequate renal function can depend upon renal prostaglandin synthesis, INDOCID P.D.A. as a prostaglandin inhibitor, may precipitate renal insufficiency, including acute renal failure, especially in neonates with other conditions that may adversely affect renal function (e.g., extracellular volume depletion from any cause, congestive heart failure, sepsis, concomitant use of any nephrotoxic drug, hepatic dysfunction). When significant suppression of urine volume occurs after a dose of INDOCID P.D.A., no additional dose should be given until the urine output returns to normal levels (see CONTRAINDICATIONS).

INDOCID P.D.A. in preterm infants may suppress water excretion to a greater extent than sodium excretion. This may result in hyponatremia. Renal function and serum electrolytes should be monitored (See DOSAGE AND ADMINISTRATION).

Central Nervous System Effects

Prematurity per se, is associated with an increased incidence of spontaneous intraventricular hemorrhage, however, because indomethacin inhibits platelet aggregation, the potential for intraventricular bleeding may be increased. A number of intracranial hemorrhages have been reported in infants who received INDOCID P.D.A. However, in one multicenter study of INDOCID P.D.A. involving 405 infants, the incidence of intraventricular hemorrhage in neonates treated with INDOCID P.D.A. was not significantly higher than in the control neonates.

Gastrointestinal Effects

Clinical results indicate that major gastrointestinal bleeding was no more common in those neonates receiving indomethacin than in those neonates on placebo. However, gastrointestinal bleeding (i.e. chemical detection of blood in stool) was more commonly noted in those neonates treated with indomethacin. Severe gastrointestinal effects have been reported in adults with various arthritic disorders treated for a prolonged period with oral indomethacin.

The following have been reported with oral use of indomethacin in adults and could occur in infants on intravenous indomethacin: irritation of the gastrointestinal tract and single or multiple gastrointestinal ulcerations. Fatalities have been reported in some instances. Rarely, intestinal ulceration has been associated with stenosis and obstruction.

Because of the occurrence, and at times severity, of gastrointestinal reactions to indomethacin the prescribing physician must be continuously alert for any sign or symptom signaling a possible gastrointestinal reaction. The risks of continuing therapy with indomethacin in the face of such symptoms must be weighed against the possible benefits to the individual patient.

PRECAUTIONS

Indomethacin may mask the usual signs and symptoms of infection. Therefore, the physician must be continually on the alert for this and should use the drug with extra care in the presence of existing controlled infection.

Severe hepatic reactions have been reported in adults treated for a prolonged period with oral indomethacin for arthritic disorders. If clinical signs and symptoms consistent with liver disease develop in the neonate, or if systemic manifestations occur, INDOCID P.D.A. (indomethacin sodium for injection) should be discontinued.

Indomethacin, like other non-steroidal anti-inflammatory agents, can inhibit platelet aggregation. Premature infants should be observed for signs of bleeding. Indomethacin has been shown to prolong bleeding time (but within the normal range) in normal adult subjects. This effect may be exaggerated in patients with underlying hemostatic defects (see CONTRAINDICATIONS).

The drug should be administered carefully to avoid extravascular injection or leakage as the solution may be irritating to tissue.

Drug Interactions

Digitalis

Preterm infants with patent ductus arteriosus and associated cardiac failure are frequently treated with digitalis. The half-life of digitalis in preterm infants is generally prolonged, and renal function during therapy with indomethacin is often reduced. Where both drugs are used concomitantly, the neonate should be observed closely; frequent ECGs and serum digitalis levels may be required to prevent or to detect digitalis toxicity early.

Furosemide

Therapy with indomethacin may decrease the natriuretic effect of furosemide.

Aminoglycosides
In one study of premature infants treated with INDOCID P.D.A. and also receiving either gentamicin or amikacin, both peak and trough levels were significantly elevated for both antibiotics.

Furosemide/Thiazide Diuretics
Clinical studies in adults have shown that the administration of indomethacin can reduce the natriuretic and anti-hypertensive effects of furosemide and thiazides in some patients. This response has been attributed to inhibition of renal prostaglandin synthesis by non-steroidal anti-inflammatory drugs. Therefore, when INDOCID P.D.A. is added to the treatment of an infant receiving furosemide or thiazides, or furosemide or thiazides are added to the treatment of an infant receiving INDOCID P.D.A., the patient should be observed closely to determine if the desired effect of furosemide or thiazides is obtained.

Anticoagulants
Indomethacin usually does not influence the hypoprothrombinemia produced by anticoagulants. When indomethacin is added to anticoagulants, prothrombin time should be monitored closely. In post marketing experience, bleeding has been reported in patients on concomitant treatment with anticoagulants and INDOCID. Caution should be exercised when INDOCID and anticoagulants are administered concomitantly.

Antihypertensive agents
In some patients with compromised renal function, the co-administration of an NSAID and an ACE inhibitor or angiotensin II antagonist may result in further deterioration of renal function, including possible acute renal failure, which is usually reversible.

ADVERSE REACTIONS

In a collaborative double-blind placebo-controlled trial of 405 premature infants weighing less than or equal to 1750 g with evidence of large ductal shunting, there was a statistically significantly greater incidence of bleeding problems in those neonates treated with INDOCID P.D.A. (indomethacin sodium for injection) than in those treated with placebo. Specifically, these bleeding disorders included gross or microscopic bleeding into the gastrointestinal tract, oozing from the skin after needle puncture, pulmonary hemorrhage, microscopic hematuria and disseminated intravascular coagulopathy. There was no statistically significant difference between treatment groups with reference to intracranial (e.g., intraventricular) hemorrhage.

The neonates treated with indomethacin sodium for injection also had a significantly higher incidence of transient oliguria and hypercreatininemia (≥1.8 mg/dL [≥159 µmol/L]) than did the neonates treated with placebo.

The incidence of retrolental fibroplasia (grades III and IV) and pneumothorax in neonates treated with INDOCID P.D.A. were no greater than in placebo controls and were statistically significantly lower than in surgically-treated infants.

The following additional adverse reactions in neonates have been reported from the collaborative study, anecdotal case reports, and from other studies using rectal, oral, or intravenous indomethacin for treatment of patent ductus arteriosus.

CARDIOVASCULAR
Pulmonary hypertension, intracranial bleeding

GASTROINTESTINAL
Gastrointestinal bleeding, abdominal distension, vomiting, melena, transient ileus, gastric perforation, localized perforation(s) of the small and/or large intestine, and necrotizing enterocolitis.

LABORATORY FINDINGS

Hyponatremia, elevated serum creatinine, elevated serum potassium, elevated BUN, decreased platelet aggregation, and reduction in blood sugar including hypoglycemia.

General: increased weight gain (fluid retention); exacerbation of infection.

Renal: renal failure; renal dysfunction including one or more of the following: reduced urinary output; reduced urine sodium, chloride, or potassium, urine osmolality, free water clearance, or glomerular filtration rate; uremia.

The following adverse reactions have also been reported in neonates treated with indomethacin, however, a causal relationship to therapy with INDOCID P.D.A. has not been established.

Cardiovascular: bradycardia.

Respiratory: apnea, exacerbation of pre-existing pulmonary infection.

Hematologic: disseminated intravascular coagulation, thrombocytopenia.

Metabolic: acidosis/alkalosis.

Ophthalmic: retrolental fibroplasia.

For ADVERSE REACTIONS which have been reported in adults please consult the Prescribing Information for INDOCID (indomethacin sodium for injection).

DOSAGE AND ADMINISTRATION

FOR INTRAVENOUS ADMINISTRATION ONLY.

Dosage recommendations for closure of the ductus arteriosus depend on the age of the infant at the time of therapy. A course of therapy is defined as from one up to three intravenous doses of INDOCID P.D.A. (indomethacin sodium for injection) given at 12-24 hours intervals, with careful attention to urinary output. If anuria or marked oliguria (urinary output 0.6 mL/kg/hr) is evident at the scheduled time of the second or third dose of INDOCID P.D.A., no additional doses should be given until laboratory studies indicate that renal function has returned to normal.

If severe adverse reactions occur, STOP THE DRUG.

Dosage according to age is as follows:

AGE at 1st dose	**DOSAGE (mg/kg)**		
	1st	**2nd**	**3rd**
<48 hours	0.2	0.1	0.1
2 - 7 days	0.2	0.2	0.2
Over 7 days	0.2	0.25	0.25

If the ductus arteriosus closes or is significantly reduced in size after an interval of 48 hours or more from completion of the first course of INDOCID P.D.A., no further doses are necessary. If during continued medical management the ductus arteriosus re-opens, a second course of 1-3 doses may be given, each dose separated by a 12-24 hour interval as described above (in the U.S. collaborative study about 10% of the infants required a second course of therapy).

If the infant remains unresponsive to therapy with INDOCID P.D.A. after 2 courses,

surgery may be necessary for closure of the ductus arteriosus.

Directions for Use

The solution may be prepared only with 2 mL of preservative-free sterile sodium chloride injection 0.9% or sterile, preservative-free water for injection. Benzyl alcohol as a preservative has been associated with toxicity in neonates. Therefore, all diluents should be preservative-free. With 2 mL of diluent the concentration of the solution will equal approximately 0.05 mg/0.1 mL. Any unused portion of the solution should be discarded because there is no preservative contained in the vial. A fresh solution should be prepared just prior to each administration. Once reconstituted, the indomethacin solution may be injected intravenously. While the optimal rate of injection has not been established, published literature suggests an infusion rate over 20-30 minutes.

Parenteral drug products should be inspected visually for particulate matter and discolouration prior to administration whenever solution and container permit.

INDOCID P.D.A. is not buffered. Further dilution with I.V. infusion solutions is not recommended.

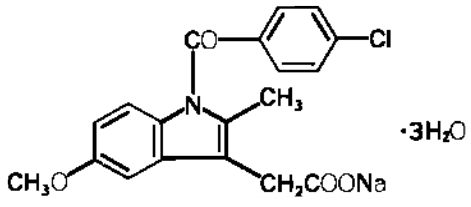
Overdosage

There are no specific measures to treat acute overdosage with INDOCID P.D.A. The patient should be followed for several days because gastrointestinal ulceration and hemorrhage have been reported as adverse reactions of indomethacin. In case of accidental drug overdose, contact your regional Poison Control Centre.

PHARMACEUTICAL INFORMATION

Indomethacin sodium trihydrate is designated chemically as 1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indole-3-acetic acid, sodium salt, trihydrate.

Structural Formula



Empirical Formula $C_{19}H_{15}ClNNaO_4 \cdot 3H_20$

Molecular Weight 433.82

Description Pale yellow crystalline powder

pKA and pH values The pKA is 4.5. The pH of a 1% solution is 8.4.

Solubility Very soluble in methanol; soluble in water, ethanol. Very slightly soluble in chloroform, acetone.

AVAILABILITY OF DOSAGE FORMS

INDOCID P.D.A. (indomethacin sodium for injection) for intravenous administration contains only sterile, lyophilized indomethacin sodium trihydrate. Each single dose vial contains indomethacin sodium trihydrate equivalent to 1.0 mg indomethacin. Supplied in boxes of 3 as a white to yellow lyophilized cake or plug. Store at room temperature (15^{o}C-30^{o}C). Protect from light. Store vials in carton until contents have been used.

PHARMACOLOGY

Although the exact mechanism of action through which indomethacin sodium causes closure of a patent ductus arteriosus is not known, it is believed to be through inhibition of prostaglandin synthesis. Indomethacin has been shown to be a potent inhibitor of prostaglandin synthesis, both in vitro and in vivo. In human newborns with certain congenital heart malformations, PGE 1 dilates the ductus arteriosus. In fetal and newborn lambs, E type prostaglandins have also been shown to maintain the patency of the ductus, and as in human newborns, indomethacin causes its constriction.

Studies in healthy young animals and in premature infants with patent ductus arteriosus indicated that, after the first dose of intravenous indomethacin, there was a transient reduction in cerebral blood flow velocity and cerebral blood flow. Similar decreases in mesenteric blood flow and velocity have been observed. The clinical significance of these effects have not been established.

In double-blind placebo-controlled studies of indomethacin sodium for injection in 460 small preterm infants, weighing 1750 g or less, the neonates treated with placebo had a ductus closure rate after 48 hours of 25 to 30%, whereas those treated with indomethacin sodium for injection had a 75 to 80% closure rate. In one of these studies, a multicenter study, involving 405 preterm neonates, later re-opening of the ductus arteriosus occurred in 26% of infants treated with indomethacin sodium for injection, however, 70% of these closed subsequently without the need for surgery or additional indomethacin.

In a study of 19 premature infants with patent ductus arteriosus treated with either indomethacin sodium for injection alone or a combination of indomethacin sodium

for injection and furosemide, results showed that neonates receiving both drugs had significantly higher urinary output, higher levels of sodium and chloride excretion, and higher glomerular filtration rates than did those neonates receiving indomethacin sodium for injection alone. In this study, the data suggested that therapy with furosemide helped to maintain renal function in the premature infant when indomethacin sodium for injection was added to the treatment of patent ductus arteriosus.

TOXICOLOGY

Acute Toxicity

The acute oral toxicity of indomethacin sodium trihydrate was studied in male and female mice. The LD_{50} (based on a 14-day mortality response was 21 mg/kg for male mice and 37 mg/kg for female mice). No signs of toxicity were seen in the first 24 hours. However, in two to three days, ataxia, decreased activity and a generally weakened condition were seen at doses of 20 mg/kg and above. Deaths occurred in two to seven days in the male mice and overnight to eleven days in the female mice.

The oral LD_{50} value in female mice for indomethacin is 50 mg/kg. Time of death and clinical signs are similar to those seen with indomethacin sodium trihydrate.

These data suggest that the acute toxicity of indomethacin sodium trihydrate is similar to that of indomethacin.

Indomethacin has been given to nine species of animals in short and long term studies. However with the exception of pigs and chickens, the human dose is not tolerated. The main toxic signs exhibited are inflammation and/or ulceration of the gastrointestinal mucosa and diarrhea.

Reproduction and Teratogenicity

In rats and mice, oral indomethacin 4 mg/kg/day given during the last three days of gestation caused a decrease in maternal weight gain and some maternal and fetal deaths. An increased incidence of neuronal necrosis in the diencephalon in the live-born fetuses was observed. At 2 mg/kg/day, no increase in neuronal necrosis was observed as compared to the control groups. Administration of 0.5 or 4 mg/kg/day during the first three days of life did not cause an increase in neuronal necrosis at either dose level.

Pregnant rats, given 2 mg/kg/day and 4 mg/kg/day during the last trimester of gestation, delivered offspring whose pulmonary blood vessels were both reduced in number and excessively muscularized. These findings are similar to those observed in the syndrome of persistent pulmonary hypertension of the neonate. Studies in mice demonstrated that indomethacin crosses the placental barrier.

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Imported by: McKesson Logistics Solutions,
Mississauga, Ontario, Canada L5R 3Y4

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Last Revision: January 26, 2010