

Kofinas Perinatal

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Patient instructions for the use of Indomethacin and Procardia (Nifedipine) in the treatment of preterm labor

Indomethacin

Indomethacin is an arthritis medication (non-steroidal anti-inflammatory) that is a potent tocolytic (medication to stop uterine contractions and labor) especially in the first 28 weeks of gestation when other medications are less potent. Indomethacin is used in patients with early cervical shortening with or without visible contractions. The reason for its use is to stop the production of cytokines (potent chemicals) that can initiate labor and / or premature cervical shortening, which may lead to either pregnancy loss, or extreme prematurity with severe neonatal consequences. (See Exhibit I; page 4)

At Kofinas Perinatal, the use of Indomethacin plays a dual role; diagnostic and therapeutic. In patients with cervical shortening, the indiscriminate use of cervical cerclage has not been shown to make a difference in the pregnancy outcomes. The reason for this failure of the cerclage is the presence of preterm labor. Failure to recognize and properly treat labor, leads almost always to pregnancy loss and/or preterm delivery. If Indomethacin restores cervical length to normal, then preterm labor is the most likely reason for the cervical shortening. In such cases, continuation of tocolysis (anti-contraction medications) maintains the pregnancy and leads to term delivery. In contrast, when the cervix is not restored and/or when the cervix shortens further, the reason for the shortening is cervical tissue weakness (cervical incompetence) and cerclage is indicated and successful in almost 98 % of the patients. Because most of the patients with cervical incompetence suffer from variable degrees of preterm labor, we continue to treat these patients with tocolytic (anti-contraction) medications. (Indomethacin and Procardia).

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Maternal side-effects

The vast majority of our patients have not experienced any side effects. Occasionally, Indomethacin like all anti-inflammatory agents, may be associated with gastric irritation and it is advisable to be taken with food or some antacid (Mylanta, etc.) if such irritation is present. Otherwise, maternal complications are very unlikely with the exception of allergic reactions. Some patients have experienced light headache which is very unusual since Indomethacin is very much like Motrin which is used for headaches. Some patients may experience water retention, which may manifest in the form of swelling in the legs and/or hands. This usually happens when in patients who take the medication for more than 5-10 days. Our protocols are usually limited to 3-7 days and we have never had an occasion where we needed to stop the treatment because of swelling. In any case, there has been no instance in my 12-year experience of using Indomethacin where I needed to stop the medication due to any side effects (with the exception of allergy); such experience is very encouraging considering that the alternative would be to admit the patient to the hospital for intravenous (IV) treatment with Magnesium Sulfate.

Fetal side-effects

Up to date evidence in the international literature indicates that the use of Indomethacin for premature labor is safe for the fetus and the concerns that have been expressed at times by some studies have not been substantiated. Of importance, is the fact that prior to 24 weeks, pregnancy loss or extreme prematurity is the alternative to not using Indomethacin. The most significant concern about its side-effects is the premature closure of the ductus arteriosus. This is the vessel that in fetuses, takes the blood from the right ventricle directly into the aorta bypassing the lungs. This vessel must be open during the pregnancy and closes after the baby is born. Premature closure may lead to pulmonary hypertension. This condition has been described in a very small number of fetuses that were exposed to Indomethacin after **34 weeks gestation**. This is very important because the ductus arteriosus becomes increasingly prone to closure as the baby approaches term (40 weeks) since it is supposed to close as soon as the baby is born. To our knowledge, there is no data to indicate that premature closure of the vessel has been reported in pregnancies prior to 32 weeks.

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In our experience of more than 14 years of using the medication, no fetus has ever experienced complete ductus arteriosus closure even in dosages 4-5 times our current protocol.

However, because of the theoretical risk and because we do not want your baby to be the first one to experience such a complication, we assess the baby's ductus arteriosus with high resolution sonography, color Doppler and PW Doppler measurements prior to the initiation of the treatment and every 3-4 days as necessary there after. Usually we use the medication only for short periods of time and **absolutely** only when we have to.

The alternative to Indomethacin would be intravenous Magnesium Sulfate which requires hospitalization and which can be lethal to the mother if the infusion pump is set inappropriately or the pump malfunctions. The benefits and risks of Indomethacin favor its use and we certainly prefer it to Magnesium. In addition the cost effectiveness of Indomethacin far outweighs the use of Magnesium.

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Indomethacin administration schedule

Oral administration:

Usually the starting oral dose is four-to-eight 25 mg capsules a day given in divided doses of one to two capsules every 6 hours. Usually we start the patient on 8 caps a day and then adjust according to the patient's response. We prefer the 6am 12 noon, 6pm and 12 midnight schedule.

Patients who take 8 caps a day (two 25 mg capsules every 6 hours) will follow the schedule below:

6 am (2 caps) 12 noon (2 caps) 6 pm (2 caps) 12 midnight (2 caps).

Patients who take 6 caps a day will follow the schedule below:

6 am (1 caps) 12 noon (2 caps) 6 pm (1 caps) 12 midnight (2 caps).

Patients who take 4 caps a day will follow the schedule below:

6 am (1 caps) 12 noon (1 caps) 6 pm (1 caps) 12 midnight (1 caps).

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Procardia (Generic name: Nifedipine)

Nifedipine is a smooth muscle relaxant and belongs to the group of the Calcium channel blockers. It is primarily used for cardiac conditions (arrhythmias and hypertension). It has been also used to treat fetal arrhythmias in utero. It is a clinically safe and efficacious tocolytic (stops uterine contractions) with minimal maternal side effects. There are no known fetal side effects that may preclude its use on a risk to benefit ratio.

The most severe side effect reported by most of our patients is some light-headedness which is primarily due to a mild hypotensive effect. This symptom has been significant to force us to discontinue the medication only a few times in the last 2-3 years. Most patients get used to this symptom and tolerated the medication well afterwards.

Occasionally, we temporarily reduce the dosage for a few days and then resume the normal dosage with no side effects. There is no need for fetal assessment because of Nifedipine.

Some patients may experience mild tachycardia (increased heart rate). This is the result of the mild hypotension caused by the medication and is usually self-limited. If not, then the medication will be reduced or discontinued.

Procardia dosage and administration schedule

We prescribe the following formulation:

Nifedipine XL 30 mg: to be administered according to the schedule below.

2 tablets twice a day every 12 hours.

The maximum dosage is for a total of 200 mg a day. Typically, most patients do well with 120 mg a day and only rarely we need to give more. Occasionally, we give an additional tablet in the early afternoon between the morning and evening dosage.

Usually, we start Procardia after the Indomethacin as a maintenance treatment and continue it for as long as the patient does well. If the cervix gets shorter then we go back

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to Indomethacin for a period of 2 to 7 days. This alternate usage goes on until 30-32 weeks and after that, most patients do well with Procardia only.

When the cervix gets shorter in less than two weeks of Procardia, we found that many patients do well with an alternating schedule of Indomethacin and Procardia on a weekly pattern as follows: Procardia during the five working days of the week and Indomethacin during the weekend. Due to the short fetal exposure to Indomethacin, we can use this dosaging scheme until 32-33 weeks with no fetal side effects. Fetal ductus arteriosus is indicated in such patients on a weekly basis.

All treatments for preterm labor are stopped at 37 weeks unless otherwise indicated.

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Exhibit I

The Length Of The Cervix And The Risk Of Spontaneous Premature Delivery

In 2915 pregnant women examined by transvaginal sonography, the average cervical length was found to be 35.2 ± 8.3 mm (10th % =22 mm and the 90th%=48 mm) and 33.7 ± 8.5 mm at 24 and 28 weeks respectively. The cervical length was normally distributed in both gestational ages. The overall rate of preterm delivery prior to 35 weeks gestation in the group was 4.3 %. With this as a reference point relative risks and absolute percent risks are given in the following table for patients examined at 24 weeks:

| Cervical length | RR for delivery<35 wks | % risk for delivery<35 wks |
|------------------------|----------------------------------|--------------------------------------|
| <40 | 1.98 | 8 % |
| <35 | 2.35 | 10 % |
| <30 | 3.79 | 16 % |
| <26 | 6.19 | 26 % |
| <22 | 9.49 | 40 % |
| <13 | 19.99 | 86 % |

In patients examined at 28 weeks and beyond, the relative risk is 2.80, 3.52, 5.39, 9.57, 13.88, and 24.94 respectively.

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