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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. *{Berghella, V., et al. Am J Obstet Gynecol, 2004. 191(4): p. 1311-7}*. 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 after one week of treatment, 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 after one week of treatment, the reason for the shortening is cervical tissue weakness (cervical insufficiency) 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).

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, Tums, Zantac, Pepcid, 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 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 15-year experience of using Indomethacin where I needed to stop the medication due to any side effects (with the exception of allergy and idiosyncratic reactions); 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

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(40 weeks). To our knowledge, there is no data to indicate that premature closure of the vessel has been reported in pregnancies prior to 32 weeks when treated with short courses of Indomethacin for tocolysis.

In our experience of more than 17 years of using the medication, no fetus has ever experienced complete ductus arteriosus closure even in dosages 4-5 times our current protocol. However, spontaneous constriction or even closure of the ductus has happened in the past and may happen to any baby for reasons that are not clear. Also, patients receiving medications similar to Indomethacin for prolonged periods of time (> 2 weeks) have experienced premature ductal constriction.

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 3-7 days as necessary thereafter. 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. In addition, neonates born after intrauterine exposure to Magnesium Sulfate have increased mortality according to cord blood levels of Magnesium. The higher the magnesium levels at birth the higher the neonatal mortality. 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 considering the high cost of prolonged maternal hospitalization.**

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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 and there is no need for fetal assessment because of Nifedipine.

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 7 years. Most patients get used to this symptom and tolerate the medication well. Occasionally, we temporarily reduce the dosage for a few days and then resume the normal dosage with no side effects. 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. Finally, some patients may notice (especially when they stand up) that their lower extremities become red. This is a physiologic (normal) response to the vasodilatory effects of the medication on the venous muscle. This does not affect any of the normal functions of the patient and has no clinical consequences. Therefore, patients are urged to ignore it and if they wish, they may call the office to discuss the symptoms with Dr. Kofinas.

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Procardia dosage and administration schedule

We prescribe the following formulation:

Nifedipine XL 30 mg tabs or Nifedipine XL 60 mg tabs

If we have a choice we prefer the 30 mg tabs because if necessary, we can add one 30 mg tablet in the early afternoon. Some patients such as twin and triplet gestations require more medication due to increased blood volume and dilutional effect. However, some insurance companies allow us to use only the 60 mg tabs.

Two 30 mg tabs or one 60 mg tab 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 (well below the maximum dosage) 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 while on Procardia, then we either use one more course of Indomethacin for seven days or continue the Procardia and add Indomethacin for the weekend only (for two days only every week). 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 daily according to schedule noted above with the addition of Indomethacin during the weekend only (the patients takes a total of 8 dosages of Indomethacin on Saturday and Sunday). For the weekend the patients take both Procardia and Indomethacin. 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 evaluation with color and PW Doppler imaging is indicated in such patients on a weekly basis. When we stop the use of Indomethacin, the follow up visits are every two weeks.

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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