

CIRCULAR

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PROTOCOLS FOR ADMINISTRATION OF TOCOLYTIC AGENTS (INTRAVENOUS SALBUTAMOL or ORAL NIFEDIPINE) FOR THREATENED PRETERM LABOUR ²

Introduction

These protocols were developed by the NSW Pregnancy and Newborn Services Network's High Risk Obstetric Advisory Group. The protocols are based on NHMRC recommendations¹, have been endorsed by the NSW Maternal and Perinatal Committee, and are now issued as policy by NSW Health.

The intended users of these protocols are medical staff, midwives, registered nurses, and Air Ambulance and Royal Flying Doctor Service flight nurses in emergency obstetric situations.

These protocols should only be used in consultation with specialists who are familiar with the management of preterm labour and the care of preterm infants.

All maternity units should have in place similar protocols that provide for safe, controlled administration of salbutamol (in low volumes of intravenous fluid) and oral nifedipine.

Aim of tocolysis

The aim of tocolysis is to delay preterm delivery to allow time for maternal administration of corticosteroids and in-utero transfer to a tertiary perinatal centre, thereby reducing neonatal morbidity and mortality ²

In other circumstances tocolysis should be used only rarely and for period not exceeding 48 hours, as there is no clear evidence that *prophylactic or maintenance* tocolytic drugs improve outcome following *threatened* preterm labour ²

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In accordance with the provisions incorporated in the Accounts and Audit Determination, the Board of Directors, Chief Executive Officers and their equivalents, within a public health organisation, shall be held responsible for ensuring the observance of Departmental policy (including circulars and procedure manuals) as issued by the Minister and the Director-General of the Department of Health.

Indications for tocolytics

Preterm delivery is a major cause of perinatal morbidity and mortality¹. Tocolytic agents are effective in reducing the likelihood of delivery within 48 hours, but do not reduce the overall risk of preterm delivery.

Consideration should be given for the administration of tocolytics to all women experiencing preterm labour when there is a need to delay delivery^{2, 3}:

- to permit in-utero transfer to a tertiary perinatal centre for multidisciplinary management (obstetrician, neonatologist, anaesthetist); and / or
- to gain up to 48 hours to allow for the administration of corticosteroids to enhance pulmonary maturity.

Where there is doubt about the use of tocolytic agents and where maternal transfer is indicated, early consultation with a tertiary obstetric unit should be made to discuss management options.

If there are clinical indications for the use of tocolysis, corticosteroids should be given as per NHMRC guidelines¹. Note that glucose homeostasis may be disturbed by corticosteroids and should be monitored.

Choice of tocolytic agent²

Beta-sympathomimetics - salbutamol

These are the most widely used tocolytics and have been extensively studied in randomised controlled trials. Salbutamol has been the most widely used beta-sympathomimetic in Australia and was recommended by the NHMRC in its 1996 report¹. It must be given intravenously, it has several maternal contraindications and significant maternal side effects.

Recently more information has become available from trials comparing nifedipine (a calcium antagonist) atosiban (an oxytocin antagonist) and indomethacin (a prostaglandin antagonist) with beta-mimetics.

Calcium antagonists – nifedipine

Nifedipine is an equally effective tocolytic, as shown by a recent Cochrane Review⁴. It is administered orally and has fewer maternal side effects. However, nifedipine is not approved for use in pregnancy and is classified as a risk Category C drug by the Australian Drug Evaluation Committee⁵.

Oxytocin antagonists - atosiban

Atosiban appears to be as effective as beta-mimetics. It has fewer maternal side effects but is much more expensive than other options in preterm labour². However, it is not approved for use in Australia.

Prostaglandin antagonists – indomethacin

Indomethacin has been compared in small trials with beta-mimetics. These have suggested equal efficacy in delaying preterm birth but there are concerns about adverse effects on the fetal circulation.

Other agents – glyceryl trinitrate

Glyceryl trinitrate patches have been evaluated in a small number of women and there is insufficient evidence to support use in routine clinical practice ².

Clinicians should ensure their choice of agent is informed by the balance of evidence, as well as their experience in use of a given agent and in the light of advice from clinicians at the receiving hospital. Choice of tocolytic drug is also discussed in a recent RCOG draft evidence-based guideline for the use of tocolytics.

Contraindications and side effects of tocolytics

Contraindications, side effects and sample administration protocols for salbutamol and for nifedipine are provided below. Concurrent use of salbutamol and vasodilators such as nifedipine should be avoided if possible, due to theoretical concerns about possible interaction and risk of potentiation of antihypertensive effect.

Prior to administration of either drug, the mother should be informed of the need to administer a tocolytic as well as the anticipated benefits and the possible maternal and fetal side effects of the agent to be used.

Salbutamol

Maternal contraindications

- Cardiac disease
- Hyperthyroidism
- Uncontrolled maternal diabetes mellitus

Fetal contraindications

- Placenta abruptio or significant uterine bleeding of unknown cause
- Fetal death or major fetal malformation
- Chorioamnionitis

Maternal side effects

- Beta-sympathomimetics are not utero-specific and have significant cardiovascular and other side effects (chest pain, cardiac arrhythmias, palpitations, tachycardia, hypotension, tremor, dizziness, headache, dyspnoea, nausea and vomiting).
- Several maternal deaths have been reported, which have been associated with either pre-existing cardiac disease or pulmonary oedema after excessive use of intravenous fluids.

Nifedipine

Maternal contraindications:

- Hypotension (systolic BP less than 90mmHg)
- Previous adverse reaction to calcium channel blockers
- Cardiac disease (congestive cardiac failure, aortic stenosis)
- Hepatic dysfunction
- Pre-eclampsia

Fetal contraindications:

- Suspected intrauterine infection

- Labour in the presence of placenta praevia
- Placenta abruptio / undiagnosed significant vaginal bleeding
- Severe fetal growth restriction
- Lethal fetal anomalies
- Fetal death in utero

Common side effects: palpitation, peripheral oedema, hypotension, dizziness, flushing, headache, nausea, vomiting

Rare side effects: abnormal liver function tests, congestive cardiac failure, transient hyperglycaemia, tachycardia, chest pain, ischaemia (retinal, cerebral), tinnitus, pruritis

Robert McGregor
Acting Director-General

Salbutamol Infusion Regimen – Example	
NOTE: To prevent hypotension due to aorto-caval compression, the patient should lie on her side during infusion	
PRESENTATION:	Ventolin Obstetric 5mg ampoules (1mg per ml)
ADMINISTRATION:	Salbutamol should be given by controlled infusion to control dose and fluid volume; a syringe or volumetric infusion pump is the equipment of choice Caution is required when changing to salbutamol from a vasodilator such as nifedipine, which has a half-life of 6 to 12 hours. In these circumstances, frequent maternal and fetal observations (as described below) are required.
DOSE:	<ul style="list-style-type: none"> • Draw up 10ml (10mg) of Obstetric Salbutamol in a 10ml syringe • Withdraw 10ml from a 100ml bag of Normal Saline and replace with the 10ml of Salbutamol. The resulting solution will contain 100 micrograms per ml • Start the infusion at 6ml per hour • Increase the rate by 3ml per hour every 10 minutes until there is a suitable response, either cessation of contractions or a reduction in frequency and strength of contractions • Do not exceed 30ml per hour (equivalent to 50 micrograms per minute). However, the maximum dose is determined by the individual's response and may be much less than this in some cases
If maternal pulse greater than 140 bpm or sustained fetal tachycardia (greater than 180 bpm)	<ul style="list-style-type: none"> • Slow infusion rate until pulse or fetal heart rate return below these levels
Side effects	<ul style="list-style-type: none"> • Tremor, anxiety, nausea and palpitations are likely and the woman should be warned • CEASE INFUSION if chest pain, dyspnoea or vomiting occurs
If contractions cease	<ul style="list-style-type: none"> • Maintain infusion rate for the next 6 hours and then reduce by 3 ml per hour each hour until a maintenance level is reached (3ml per hour) • Decisions about cessation of treatment will be on an individual basis and need to take into account location, steroid cover and gestational age
MATERNAL and FETAL OBSERVATION AND MONITORING	<ul style="list-style-type: none"> • Maternal blood pressure, pulse and respiratory rate following each increase in the infusion rate during the acute stabilisation phase. Observations may then be recorded less frequently, but at least 4 hourly during treatment; • If initial cardiotocograph is reactive, record fetal heart rate with doppler after each increase in the infusion rate during the acute stabilisation phase, then at least 6 hourly for first 48 hrs.

Nifedipine Administration Protocol – Example	
<i>NOTE: Nifedipine is classified as a risk Category C drug in pregnancy. It carries the potential for fetal hypoxia associated with maternal hypotension. The blood pressure lowering effect of Nifedipine may be potentiated by other antihypertensive drugs</i>	
PRESENTATION:	20mg Tablets
ADMINISTRATION:	Nifedipine tablets should be crushed to aid absorption in pregnancy. Dose may vary with clinical situation & should be titrated against tocolytic effect. Nifedipine is highly light sensitive. Broken tablets should not be used
INITIAL DOSE:	<ul style="list-style-type: none"> • 20mg Nifedipine (crushed) orally stat
MAXIMUM DOSE	<ul style="list-style-type: none"> • 160mg in 24 hours
<i>If uterine contractions persist after 30 minutes:</i>	<ul style="list-style-type: none"> • A further 20mg Nifedipine (crushed) orally may be given at 30 minute intervals for two further doses
<i>If contractions cease</i>	<ul style="list-style-type: none"> • A maintenance dose of 20 to 40mg Nifedipine 6 hourly may be given, depending on uterine activity and other clinical circumstances, to a maximum of 160mg in 24 hours • Decisions about cessation of treatment will be on an individual basis and need to take into account location, steroid cover and gestational age
<i>Side effects</i>	<ul style="list-style-type: none"> • Hypotension, especially in hypertensive patients • Tachycardia, palpitations • Flushing • Headaches, dizziness • Nausea
MATERNAL and FETAL OBSERVATION AND MONITORING	<ul style="list-style-type: none"> • Maternal blood pressure, temperature, pulse and respiratory rate hourly during the acute stabilisation phase. Observations may then be recorded less frequently but at least 4 hourly during treatment • Report systolic BP less than 100 mmHg, temperature greater than 37.5 degrees Celsius or pulse greater than 100 • Report side effects listed above • If initial cardiotocograph is reactive, record fetal heart rate hourly with doppler during the acute stabilisation phase, then at least 6 hourly for first 48 hrs
Overdosage Symptoms (observed in cases of severe nifedipine intoxication)	<ul style="list-style-type: none"> • Disturbed consciousness to the point of coma • A drop in blood pressure • Tachycardic / bradycardic heart rhythm disturbances • Hyperglycaemia • Metabolic acidosis • Hypoxia • Cardiogenic shock with pulmonary oedema

This Circular is due for revision:

Two years from release date, by the NSW Pregnancy & Newborn Services Network

This Circular supersedes Patient Matters Manual Part II, Section 17.4 - Suppression of premature labour

This Circular should be read in conjunction with:

Circular No 99/86: *Maternity emergencies* (Patient Matters Manual Part I Section 6.18)

Circular No 99/71: *Policy for emergency obstetric and neonatal referrals* (Patient Matters Manual Part 1 Section 6.16)

NSW Midwives Association (1998). *Maternity Emergency Guidelines for Registered Nurses*. I Coonan, A Grieve, M Williamson (Eds). Sydney.

Circular No 97/106 and 97/140: *Hypertension in Pregnancy* (Patient Matters Manual Part III Section 17.13)

Circular No 01/64: *Policy on the Handling of Medication in NSW Public Hospitals* (Patient Matters Manual Part III Section 20.1)

Circular No 89/95: *Medical retrieval* (Patient Matters Manual Part III Section 25.6) (under review)

Circular No 83/116: *Administration by Nurses of Intravenous Medication* (Patient Matters Manual Part II Section 15.3)

References

¹ NHMRC and Quality of Care and Health Outcomes Committee (1996). *Clinical practice guidelines: care around preterm birth*. Canberra, AGPS. Available at <http://www.health.gov.au/hfs/nhmrc/publicat/synopses/cp51syn.htm>

² Duley, LMM, Tocolytic Drugs for Women in Preterm Labour. Guideline No 1(B) May 2001, RCOG, London. Available at URL <http://www.rcog.org.uk/guidelines/tocolytic.html>

³ Roberts, Christine L, David Henderson-Smart, David A Ellwood and the High Risk Obstetric and Perinatal Advisory Working Group (2000), Antenatal transfer of rural women to perinatal centres, *Aust NZ J Obstet Gynaecol*; 40:4: 377-384.

⁴ King JF, Flenady V, Papatsonis D, Dekker G, Carbonne B. Calcium channel blockers for preterm labour . In: The Cochrane Database of Systematic Reviews, Issue 2, 2002. Update Software, Oxford.

⁵ Australian Drug Evaluation Committee (2001) *Prescribing medicines in pregnancy: an Australian categorisation of risk of drug use in pregnancy (4th Ed)*. Therapeutic Goods Administration, Commonwealth Department of Health & Aged Care, Canberra. Available at URL <http://www.amh.hcn.net.au/>