BETAMETHASONE [WEB COMMENTARY]

Use

Maternal treatment with betamethasone accelerates surfactant production by the fetal lung reducing the incidence of neonatal respiratory distress, a property it shares with dexamethasone (q.v.).

Pharmacology

The pharmacology of betamethasone and dexamethasone are very similar. See the web site commentary for observational evidence that, antenatally, betamethasone seems to be safer than dexamethasone.

Indications for antenatal Use

The seminal paper that first identified a strategy for preventing, rather than curing, surfactant deficiency was published more than thirty years ago. The first clue came from the observation that experimental lambs delivered prematurely failed to develop the respiratory problems seen in control animals if exposed to corticosteroids before delivery. A randomised placebo-controlled trial that eventually recruited more than a thousand mothers from New Zealand soon confirmed that two 12 mg IM doses of betamethasone caused a significant reduction in the incidence of respiratory distress in babies born more than eight weeks early, and a fall in neonatal mortality in all babies born more than three weeks early. Doubling this dose brought about no further improvement in outcome. No study has ever looked to see if a smaller dose might be equally effective.

It took 20 years for this strategy to gain general acceptance and, in the interim, a further 11 trials were mounted to replicate the original findings. The most recent Cochrane review of all the 21 trials ever done shows that antenatal treatment with 24 mg of betamethasone *or* dexamethasone is associated with a 40–60% reduction in the risk of neonatal respiratory distress, and with a similar reduction in cerebroventricular haemorrhage, in necrotising enterocolitis, and in early systemic infection, and that this, in turn, results in fewer deaths, and in a reduction in the cost and duration of neonatal care. Benefit 'appears to apply to babies born at all gestational ages at which respiratory distress syndrome may occur' and one recent trial showed that it also reduced problem for babies electively delivered at 37–38 weeks gestation. Babies delivered less than 24 hours after prophylaxis is started derive only limited benefit, and it is now clear that benefit wanes after a week. Twins seem to benefit just as much as singleton babies but, because they were not separately identified in many trials, the available sample size is currently too small to establish this. Giving one more dose once a week to women not delivered within 7 days further reduced the number of babies troubled by respiratory problems after birth in the Australasian (ACTORDS) trial and there were no detectable adverse effects in the 2 year survivors. Only long term follow up will show if there are any late consequences. Giving more than this delivers no additional benefit and may further retard fetal growth, while fortnightly repetition (as in the MACS trial) delivered no benefit. Delaying further prophylaxis until delivery again seems imminent can also work well (as long as delivery can then be delayed for at least 36 hours) as the Obstetrix trial showed in March 2009.

No adverse late consequence of exposure to a single course of betamethasone could be detected when the children of the mothers recruited into the first trial in New Zealand were recontacted after 30 years. Women with hypertension and fetal growth retardation were excluded from many early trials, but we now know that these babies benefit too. Use (under prophylactic antibiotic cover) was also beneficial where there has been prelabour rupture of membranes, but use in mothers with diabetes remains less well established, since treatment could affect diabetic control. Repetitive antenatal treatment slows fetal growth but the effect was too small to be detectable at discharge in most trials, and nonexistent in the most recent trial (Garite *et al.*, 2009).

Maternal prophylaxis

First course of treatment: Give 12 mg of betamethasone *base* as a deep IM injection, and a second dose after 24 hours while trying to delay delivery for 48 hours. Oral treatment cannot be recommended on the basis of the only small trials conducted to date. While prophylaxis is of no proven benefit when delivery threatens before 24 weeks gestation, it should not be denied to those at risk of delivery at 23 weeks if requested.

Repeat treatment: If delivery does not occur for 7 days and then again becomes likely in the next 7 days, consider giving another 12 mg dose and try to delay delivery for 24 hours, since respiratory problems and their complications can be serious after delivery before 30 weeks gestation (and a reducible risk before 33 weeks).

Supply

Celastone®, a product that contains both betamethasone sodium phosphate and the more long acting ester betamethasone acetate, was used in all the more important perinatal trials, but this product is still not on sale in the UK. Indeed, the only formulation routinely available in the UK is a 1 ml ampoule containing 5·3 mg of betamethasone sodium phosphate (4 mg of betamethasone base) costing £1·20, and the ampoules provided by some manufacturers contain sodium metabisulphite. 500 microgram (5p) tablets are also available.

References

See also the relevant Cochrane reviews and UK guideline © ⊗

Lee BH, Stoll BJ, McDonald SA, *et al.* Adverse neonatal outcomes with antenatal dexamethasone versus antenatal betamethasone. *Pediatrics* 2006;**117**:1503–10.

Crowther CA, Doyle LW, Haslam RR, *et al.* Outcomes a 2 years of age after repeat doses of antenatal corticosteroids. *N Engl J Med* 2007;**357**:1179–89. [RCT] (See also 1191–8, and editorial 1248–50.)

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Garite TJ, Kurtzman J, Maurel K, *et al.* Impact of a 'rescue course' of antenatal corticosteroids: a multicenter randomized placebo-controlled trial. *Am J Obstet Gynecol* 2009;**200**:248:e1–9. [RCT] (See also 217–8.)