

**National Essential Medicine List Medication Review Process**  
**Adult Hospital Level**  
**Component: Anaesthesiology**

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**Date:** 27<sup>th</sup> March 2015

**Medication:** Alfentanil

**Introduction**

Alfentanil is a potent, ultra-short acting opioid. It is an analogue of fentanyl. The time of onset is approximately 60 - 90s and duration of action is approximately 10 minutes.

**Reason for Inclusion in Essential Medicines List**

Used in anaesthesia for the following indication:

1. Reduce the hypertensive response to intubation (HRI)

**Current Essential Medicines List Alternatives**

The other opioids currently on the EML are morphine and fentanyl of which only fentanyl has been used to reduce the HRI (the onset of morphine is too slow for this purpose, the duration of action too long and the high doses required would cause significant hypotension).

However, the duration of action of fentanyl is over 45 minutes and this can be problematic for short procedures, particularly if respiratory depression must be avoided. Furthermore, studies have shown fentanyl not to be as effective as alfentanil in reducing the HRI.

Lignocaine (IV and topical spray) is on the EML and these have both been used to reduce the HRI when given IV or topically to the airway, although studies into the success of using lignocaine for this purpose have given conflicting results.<sup>12</sup> Furthermore, topical lignocaine reduces airway reflexes postoperatively which increases the risk of postoperative aspiration of gastric contents; this is particularly a problem in patients who have had emergency surgery or have delayed gastric emptying.

**Hypertensive Response to Intubation (HRI).**

This is a brief rise in blood pressure associated with laryngoscopy. It occurs within seconds of inserting a laryngoscope. The sudden rise in blood pressure can be life-threatening in patients with certain medical conditions eg pre-eclampsia, myocardial ischaemia, cerebral injury.

For example, in patients with pre-eclampsia the hypertensive response to intubation can cause acute myocardial failure and/or cerebral haemorrhage, both of which can be fatal. Maternal deaths have been attributed to failure to obtund the hypertensive response to intubation in patients with pre-eclampsia.<sup>1,2</sup>

Morphine is not appropriate to prevent this response as its speed of onset is too slow (5-10 minutes) and duration too long (3-4 hours). The high doses required would also cause marked hypotension and prolonged respiratory depression both in the patient and the neonate, if used for Cesarean section.

Fentanyl has been used to prevent the hypertensive response to intubation but doses in excess of 2-3mcg/kg are required, the onset time is 3 minutes and duration of action is 45-60 minutes.

Alfentanil has been successfully used to reduce the hypertensive response to intubation and has been safely used for this purpose in pre-eclamptic patients having general anaesthesia.

More rarely, high doses of alfentanil have been used to maintain cardiac stability in high risk patients having general anaesthesia for caesarean section.<sup>3</sup>

## 1. Articles relevant to alfentanil reducing the hypertensive response to intubation

### A. In women having Caesarean section

Author	Type of trial	Intervention	Primary Outcome	Results	Comments
Rout 1990 <sup>4</sup>	Randomised comparative trial. 40 women with severe pre-eclampsia for CS under GA. Multips, >25y old.	Alfentanil 10mcg/kg or fentanyl 2.5mcg/kg preinduction. All also received 1mg/kg lignocaine. 17 had also received magnesium (8 alfentanil, 7 fentanyl group)	Maternal BP, HR, Neonatal Apgars, blood gases,	Equivalent effects on CVS response to intubation. Rises occurred with fentanyl and alfentanil (HR 16 vs 11bpm; BP 11 vs 8mmHg) – wide variation – some increases of up to 45bpm and 47bpm and BP ↑ of 43 and 32mmHg seen for fentanyl and alfentanil respectively.	No neonatal deaths due to opioids. Alfentanil less fat soluble – suggest less neonatal effect than fentanyl. Neither drug completely attenuated the HRI in the doses used.
Allen 1991 <sup>5</sup>	Randomised double blind comparative trial. 69 women with moderate/severe pre-eclampsia for CS under GA.	Lignocaine 1.5mg/kg vs MgSO4 40mg/kg vs alfentanil 10 mcg/kg preinduction	Maternal NIBP (Dinamap & Fina pres), HR, Neonatal Apgars, blood gases	Apgars at 1 min lower with alfentanil, 5 min same. Lignocaine group greatest rise in HR and BP (25mmHg); Mg and alfentanil mean values similar – less tachycardia with alfentanil.	No difference between groups in neonatal outcome. But 25% still had SAP>180mmHg for 4 min after induction with alfentanil- none of the agents were ideal.
Ashton 1991 <sup>6</sup>	Randomised comparative trial. 40 women with severe pre-eclampsia for CS under GA. Paediatrician blinded to drugs used.	Magnesium 40mg/kg vs magnesium 30mg/kg with alfentanil 7.5mcg/kg preinduction.	Maternal BP, HR, catecholamines. Mg and alfentanil concs. Neonatal Apgars, blood gases,	Mg concs no difference. Systolic BP rise about 30mmHg less with alfentanil (P<0.05). No difference in fetal outcomes.	Previous study with alfentanil 10mcg/kg resulted in more fetal depression.
Gin et al 2000 <sup>7</sup>	Randomised control trial. Healthy 40 patients.	Elective CS. Alfentanil 10mcg/kg vs placebo	Blood pressure. Noradrenaline conc. Apgars. Umbilical O2.	BP rise less (11 vs 31 mmHg;p,0.001). Nor ad less (P<0.05), Apgars slightly less but NACS same as Umb O2 greater with alfentanil.	One neonate needed naloxone. All Apgars at 5 mins 9/10.
Sharp 2009 <sup>8</sup>	Review. Non systematic	Changes in anaesthetic drugs for CS in last 50y	N/A	Recommend short acting opioids to obtund pressor response. Important in women with cardiac or cerebrovascular disease.	Paediatrician should always be at a CS under GA and can quickly treat any respiratory depression in neonate due to opioids.

These studies show that alfentanil reduces the hypertensive response to intubation in women having Caesarean section with a low risk of transient respiratory depression in the neonate, readily corrected by injection of naloxone. In pre-eclampsia the optimum dose of alfentanil is 7.5mcg/kg with magnesium 30mg/kg.

### B. Other surgical scenarios

Author	Type of trial	Intervention	Primary Outcome	Results	Comments
Crawford 1987 <sup>9</sup>	Randomised double blind controlled trial. 44 patients. Major surgery requiring direct arterial monitoring of BP.	Alfentanil 10mcg/kg or 40 mcg/kg or saline after induction of anaesthesia with thiopentone and vecuronium, and 90s before intubation	Heart rate and BP.	Both doses prevented any increase in HR or BP with intubation. 40mcg/kg caused profound hypotension and bradycardia. More dysrhythmias in control group.	Vecuronium non-vagolytic – contributed to bradycardia and hypotension. Recommend dose of 10mcg/kg alfentanil.
Miller 1993 <sup>10</sup>	Randomised placebo controlled trial. 60 patients with no previous cardiac problems or hypertension.	Alfentanil 15/30/45mcg/kg or saline after droperidol and tubocurarine and before thiopentone and suxamthonium. Intubated after 90 secs.	HR, BP, non-invasive cardiac index and ejection fraction. Serum catecholamine levels.	Significant ↑HR, BP& SVR controls (P<0.05). EF and CI ↔. Catecholamines ↑control and dose dependent ↓up to 30mcg/kg alfentanil.	Recommended dose of 30mcg/kg to prevent rise in catecholamines and CVS parameter.
Hartley 1994 <sup>11</sup>	RCT. 60 patients for gynae surgery having fiberoptic intubation under GA	Alfentanil 10mcg/kg vs placebo.	Heart rate and BP.	Both HR and BP increases attenuated with alfentanil (both P<0.001)	Alfentanil attenuates hypertensive response to fiberoptic intubation under GA.
Kovac 1996 <sup>12</sup>	Review. Non-systematic.	Mechanism of HRI and drugs used to prevent it	Alfentanil should be given at least 1.5 min before laryngoscopy. Dose of 10mcg/kg elderly and 30 mcg/kg young and healthy.		
Khan 2013 <sup>13</sup>	Cochrane systematic review. Adults.	Drugs to prevent HRI morbidity in mortality in elective patients.	Risk of arrhythmias reduced with several agents including “narcotics” and lignocaine. Only included studies using control group. Need more studies to focus on outcomes from reducing the HRI.		

These studies show that the optimal dose of alfentanil to reduce the hypertensive response to intubation in non-obstetric patients ranges between 10mcg/kg and 30mcg/kg. The lower dose should be used for those at risk of hypotension eg the elderly, and the higher dose of up to 30mcg/kg should be used for younger patients and those most at risk of the adverse effects of a hypertensive surge or tachycardia as a result of intubation.

### C. Article comparing IV lignocaine with alfentanil in reducing the HRI

Author	Type of trial	Intervention	Primary Outcome	Results	Comments
Pathak 1990 <sup>14</sup> (Abstract)	Prospective controlled double blind study. 60 patients.	Saline, lignocaine 2mg/kg, alfentanil 15 mcg/kg, alfentanil 30mcg/kg in rapid sequence induction with thiopentone and suxamethonium	Blood pressure and heart rate during intubation	Both doses of alfentanil successful at attenuating CVS response to intubation. Lignocaine and saline both ineffective.	

This article was the only trial found comparing the effect of IV lignocaine compared with alfentanil on obtunding the hypertensive response to intubation. It shows how ineffective IV lignocaine is in comparison with IV alfentanil.

### Summary

There is evidence that alfentanil can be successfully and safely used to obtund the hypertensive response to intubation in patients requiring general anaesthesia or instrumentation of the airways. Alfentanil can be safely used in pregnant patients provided the paediatrician receiving the neonate is aware alfentanil has been given and is prepared to administer naloxone if necessary.

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<sup>1</sup>Lewis G (ed) 2007. The Confidential Enquiry into Maternal and Child Health (CEMACH). Saving Mothers' lives: reviewing maternal deaths to make motherhood safer -2003-2005. The Seventh Report on Confidential Enquiries into Maternal deaths in the United Kingdom. London: CEMACH [www.cemach.org.uk](http://www.cemach.org.uk).

<sup>2</sup> Chapter 7: Obstetric Anaesthesia. In: Saving Mothers: Second Report on Confidential Enquiries into Maternal Deaths in South Africa 1999-2001. Department of Health.

<sup>3</sup>Redfern N, Bower S, Bullock RE, Hull CJ. Alfentanil for caesarean section complicated by severe aortic stenosis. *Br J Anaesth* 1987; 59: 1309-12.

<sup>4</sup>Rout CC, Rocke DA. Effects of alfentanil and fentanyl on induction of anaesthesia in patients with severe pregnancy-induced hypertension. *Br J Anaesth* 1990; 65: 468-474

<sup>5</sup>Allen RW, James MFM, Uys PC. Attenuation of the pressor response to tracheal intubation in hypertensive proteinuric pregnant patients by lignocaine, alfentanil and magnesium sulphate. *Br J Anaesth* 1991; 66: 216-223.

<sup>6</sup>Ashton WB, James MFM, Janicki P, Uys PC. Attenuation of the pressor response to tracheal intubation by magnesium sulphate with and without alfentanil in hypertensive proteinuric patients undergoing Caesarean section. *Br J Anaesth* 1991; 67:741-747.

<sup>7</sup>Gin T, Ngan-Kee W et al. Alfentanil given immediately before the induction of anaesthesia for elective caesarean delivery. *Anesth Analg* 2000; 90: 1167-72.

<sup>8</sup>Sharp LM, Levy DM. Rapid sequence induction in obstetrics revisited. *Curr Opin Anaesthesiol* 22: 357-361.

<sup>9</sup>Crawford DC, Fell D et al. Effects of alfentanil on the pressor and catecholamine response to tracheal intubation. *Br J Anaesth* 1987; 59: 707-712.

<sup>10</sup>Miller DR, Martineau RJ et al. Effects of alfentanil on the haemodynamic and catecholamine response to tracheal intubation. *Anesth Analg* 1993; 76: 1040-6.

<sup>11</sup>Hartley M, Morris S, Vaughan RS. Teaching fiberoptic intubation. Effect of alfentanil on the haemodynamic response. *Anaesthesia* 1994; 49:335-7.

<sup>12</sup>Kovac AL. Controlling the haemodynamic response to laryngoscopy and endotracheal intubation. *J Clin Anesth* 1996; 8: 63-79.

<sup>13</sup>Khan FA, Ullah H. Pharmacological agents for preventing morbidity associated with the haemodynamic response to tracheal intubation (review). *Cochrane Database of Systematic Reviews* 2013, Issue 7. Art. No.: CD004087. DOI: 10.1002/14651858.CD004087. Pub2.

<sup>14</sup>Phatak D, Slater RM et al. Effects of alfentanil and lidocaine on the haemodynamic responses to laryngoscopy and tracheal intubation. *J Clin Anesth* 1990; 2(2): 81-5.