

Drugs

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Chapter 8

Drugs¹

8.1 Cardiovascular drugs

The key to using these drugs effectively is knowing the likely side effects, appropriate dilutions and safe bolus doses. Learn how to bolus the drugs listed in Table 8.2 (see Section 8.1.2) using a 1 ml syringe—very useful when the pumps/power fail.

Use dedicated CVP ports—one drug per port. Avoid piggy-backing several drugs together, especially when titrating a new drug infusion.

Always reduce infusions slowly and review the effect—avoid stopping these infusions suddenly as blood pressure may fall rapidly. Check infusions will not run out during transfer to and from ITU.

Table 8.1:
Commonly used drugs for rapid bolus control of hypotension in adults.

Drug	Dilution (in saline)	Bolus dose
Ephedrine 30 mg/1 ml ampoule	30 mg/5 ml	0.5–1 ml
Metaraminol (<i>Aramine</i>) 10 mg/1 ml ampoule	10 mg/20 mls	0.5–1 ml
Phenylephrine 1 mg/10 ml ampoule	1 mg/20 mls	0.5–1 ml
Methoxamine (<i>Vasoxine</i>) 20 mg/1 ml ampoule	20 mg/20 mls	0.5–1 ml

¹<http://www.nickalls.org/dick/papers/thoracic/hand-drugs.pdf>

- **Adrenaline** has both α and β effects.
- **Dobutamine** has a predominant β_1 effect (inotropic & chronotropic), with minimal effect on peripheral vascular resistance (due to its modest β_2 and α effects). Dobutamine is the only catecholamine administered as a racemic mixture. It is this mixture which results in its characteristic β_1 selectivity, since the – isomer is an α agonist, while the + isomer is an α antagonist (Zaritsky and Chernow 1988). Dobutamine may cause hypokalaemia.
- **Ephedrine** is a so-called ‘indirect’ agonist, as it causes release of catecholamines ($\alpha + \beta$) at the terminal, and hence tachyphylaxis occurs with frequent use. It causes a moderate increase in BP and HR. If ephedrine fails to have much effect,² then consider using a pure α -agonist (e.g., metaraminol, phenylephrine, noradrenaline). Avoid using ephedrine if HR > 100. For useful references regarding ephedrine and phenylephrine see Cooper (2005).
- **Isoprenaline** has almost pure β effects. Used almost exclusively to increase the heart rate in patients with acute complete heart block.
- **Metaraminol** is a pure α -agonist. An IV bolus lasts about 5–10 minutes and commonly elicits a small reflex bradycardia (therefore avoid using if bradycardia exists). Metaraminol is slightly longer acting than than phenylephrine, and is therefore better for bolus use. If you need to give multiple metaraminol boluses then consider using a noradrenaline infusion via a CVP line (see below). If no CVP line then metaraminol can be used as a 5 mg IM dose, or as a temporary slow infusion (5–10 mg in 1 litre).
- **Noradrenaline** is an almost pure α -agonist. It does actually have a very small β effect on heart rate, and, unlike metaraminol, does not cause a reflex bradycardia with bolus doses. Contrary to popular opinion, a noradrenaline infusion for supporting a normal blood pressure is generally beneficial to the kidney and renal function in sepsis (Lee *et al.* 2004; Bellomo and Giantomasso 2001). Noradrenaline is often of value both operatively and postoperatively in patients with a history of hypertension, to counteract the vasodilatory effects of anaesthesia (general and epidural) and maintain their normal preoperative blood pressure and renal function.
- **Phenylephrine** is a pure α -agonist. It seems to have a slightly shorter duration of action compared to metaraminol, but otherwise its action is essentially similar to metaraminol.
- **Terlipressin** (triglycyl-lysine-vasopressin) is a pro-drug which breaks down to the active lysine-vasopressin (Kam, Williams and Yoong 2004). Terlipressin is often used in ITU to supplement a noradrenaline infusion in septic shock (better blood pressure control, less tachycardia, better renal and gut perfusion). The dose is 1–2 mg IV (repeat 4-hourly initially); effect half-life is 6 hrs.
- **Vasopressin (ADH)** is increasingly being used in septic shock to supplement a noradrenaline infusion (see Roth 2006; Kam, Williams and Yoong 2004, Sun *et al.* 2003). Vasopressin (American Pharmaceuticals) is available in ampoules of 20 U/ml. See Table 8.2 for a suggested ‘single strength’ dilution.

8.1.1 Infusions: dilutions and use

An important but commonly overlooked aspect of practical drug delivery is the dilution. In my view the hallmark of a well chosen dilution is that, in addition to satisfying the necessary pharmaceutical requirements, it facilitates both the mental calculation and the means of infusion and safe effective bolus delivery, particularly in urgent/emergency situations.

The dilutions listed in Table 8.2 approach this ideal; they are practical and easy to remember, dosage is easy to determine without reliance on calculators or charts. Indeed, an awareness of Table 8.2 would easily have avoided the calculation error described recently by de Wildt *et al.* (2007), associated with setting up a noradrenaline infusion.

²If initial doses of ephedrine fail to have much effect, then this is usually a sign of sepsis and that noradrenaline should be used instead.

Table 8.2:

Single strength dilutions (adults): start infusion at 5 mls/hr and titrate in increments of 2 mls/hr. When bolusing adrenaline, noradrenaline or isoprenaline start with 0.1–0.2 mls, titrating amount to effect (approximate bolus dose is 1–2 mins worth of current infusion).

Drug	Dilution (in saline)	Bolus	Infusion
Dopamine Dobutamine	$\frac{3 \times \text{kg}}{1}$ mg in 50 mls	0.1–0.2 ml	1–10 mls/hr (1–10 $\mu\text{g}/\text{kg}/\text{min}$)
GTN SNP Vasopressin (ADH)	$\frac{3 \times \text{kg}}{10}$ mg in 50 mls	0.1–0.2 ml	1–10 mls/hr (0.1–1 $\mu\text{g}/\text{kg}/\text{min}$)
Adrenaline Noradrenaline Isoprenaline	$\frac{3 \times \text{kg}}{100}$ mg in 50 mls	0.1–1 ml	1–40 mls/hr (0.01–0.4 $\mu\text{g}/\text{kg}/\text{min}$)

The entries in Table 8.2 are based on the following rule, which is a simplified and more practical form of that described by Sellick (1985), namely: for a patient weighing W kg, then diluting $3 \times W$ mg of any drug in 50 mls yields a solution for which 1 ml/hr is equivalent to 1 $\mu\text{g}/\text{kg}/\text{min}$.

When initiating an infusion, use the ‘single strength’ concentration listed in Table 8.2, and start at a rate of approximately 5 ml/hr, using boluses (see Section 8.1.2) as necessary. If the patient’s condition later requires increasingly large infusion rates, then higher concentrations (e.g. double strength, quadruple strength etc) can be used instead to avoid volume overload. If the patient is ‘obviously’ septic then start with a ‘double-strength’ dilution. A useful rule-of-thumb is to increase the infusion rate in steps of about 20%, but to decrease it in smaller steps (e.g. 10%).

Although 50 ml syringe-drivers are generally used in the operating theatres, in an ITU however, where the infusions often run for long periods of time, it is generally more convenient to use larger volumes (e.g. 100 ml or 250 ml bags) in conjunction with the usual ITU infusion-delivery systems.

Example 1

A 70 kg patient requires a dobutamine infusion. The dobutamine entry in Table 8.2, shows that diluting 210 mg (3×70) in 50 ml 5% dextrose gives a concentration for which 1 ml/hr is equivalent to 1 $\mu\text{g}/\text{kg}/\text{min}$. Start the infusion at 5 mls/hr.

Example 2

A 30 kg patient requires a GTN infusion. The GTN entry in Table 8.2, shows that diluting 9 mg ($3 \times 30/10$) in 50 ml 5% dextrose gives a concentration for which 1 ml/hr is equivalent to 0.1 $\mu\text{g}/\text{kg}/\text{min}$. Start the infusion at 5 mls/hr.

8.1.2 Bolus dosage

In emergency situations it is sometimes necessary to give IV bolus doses of these drugs (typically for GTN, adrenaline, noradrenaline). Consequently, it is very important that the dilution of the maintenance infusion used should simplify this, i.e. allow an IV bolus to be given manually and quickly using a syringe, so as not to be dependent on the electronic delivery system which can sometimes fail. An important ‘feature’ of the ‘single strength’ dilutions shown in Table 8.2 is that

they facilitate the manual administration of appropriate bolus doses, quickly, safely and easily, typically using a 1 ml syringe (see examples below).

I have found empirically that an appropriate initial bolus dose is a volume roughly equivalent to 1–2 minutes worth of the current maintenance infusion (depending on the severity of the problem). In practice the 1-minute bolus volume is easily calculated since an infusion rate of 6 ml/hr is equivalent to 0.1 ml/min; a maintenance infusion rate of R ml/hr is therefore equivalent to $0.1 \times R/6$ ml in one minute. For example, a 1-minute bolus volume for an infusion running at 12 mls/hr is $0.1 \times 12/6 = 0.2$ ml. In general the bolus volume can be easily and conveniently delivered using a 1 ml syringe—always readily available on any ward. If the effect of the initial bolus is inadequate, sequentially double the bolus volume until a therapeutic bolus volume is found.

8.1.3 Noradrenaline

Example 1

Consider a 70 kg routine surgical patient requiring a noradrenaline infusion to counteract the effects of an epidural (typical requirement: single strength noradrenaline running at 2–8 mls/hr).

Step 1: Dilute $\frac{3 \times 70}{100}$ mg noradrenaline into 50 mls saline, (i.e., approximately 2 mg in 50 mls), and start the infusion at 5 mls/hr (equivalent to 0.05 $\mu\text{g}/\text{kg}/\text{min}$). Remember to include a three-way tap and a filled labelled 1 ml syringe, and connect the infusion to the central-line port as a separate dedicated infusion.

Step 2: Now fill the central-line deadspace cautiously, using 0.1–0.2 ml increments, until a bolus results in a transient rise in blood pressure. Then titrate the infusion using increments of about 2–4 mls/hr to obtain a suitable blood pressure, using small boluses via a 1 ml syringe as necessary to gain control. If the patient is significantly ‘septic’ then the infusion rate may well need to be increased, up to 50 mls/hr as necessary.³ A useful rule-of-thumb is to increase the infusion rate in steps of 20%, but to decrease it in steps of only 10%.

Notes: If there is occasion to rescue a low BP of, say, 60–70 mmHg, then a bolus of approximately 1–2 mins worth of the infusion will be an appropriate first choice test dose. For example, if the current infusion rate is 6 mls/hr then consider a test bolus of about 0.1–0.2 mls (since an infusion of 6 mls/hr is equivalent to 0.1 ml/min).

Example 2

Consider a 70 kg septic ITU patient on double-strength noradrenaline at 12 mls/hr, and suppose you are now called because the infusion has suddenly stopped, and the blood pressure is falling.

This amount of noradrenaline is not unusual in the ITU—even the use of ‘quad’ strength is not uncommon. However, what is not widely appreciated is that if a ‘high-dose’ noradrenaline infusion stops suddenly (e.g., battery failure; line occlusion; bag/syringe empty etc.) the blood pressure fall will be rapid and profound—for example, falling to about 40–50 mmHg within 1 minute or so—and so this problem constitutes a significant emergency and must be addressed immediately. The essence of the problem, therefore, is how to administer 2 minutes worth of noradrenaline to the patient within less than 1 minute from a standing start.

Step 1: Note the infusion rate:— 12 mls/hr in this case.

Step 2: Divide the current infusion rate by 6 to determine the number of 0.1 ml units the patient would normally be receiving per minute⁴ (this is the minimum bolus volume). Thus, in this example we have $12/6 = 2$, and so the ‘1-minute’ bolus volume is $2 \times 0.1 \text{ mls} = 0.2 \text{ mls}$.

³If large infusion flow rates become necessary, then consider using twice the concentration (or whatever) with an appropriately reduced rate (one can happily use a ‘single’ strength dilution up to 50 mls/hr or so in a theatre setting).

⁴An infusion of 6 mls/hr is equivalent to 0.1 mls/min.

Step 3: Fill a 1 ml syringe directly from the infusion bag/reservoir/pump and inject 2 mins worth of noradrenaline infusion as a bolus—0.4 ml in this case (2×0.2)—down a *separate*⁵ CVP/IV line and flush it in with 10 mls saline. If there is already significant bradycardia, then atropine and temporary cardiac massage may also be necessary to help the drug get around. Titrate against the blood pressure, approximately 0.2 mls/min, as necessary, until the original infusion problem is fixed and ‘up and running’ again.

Notes: In this particular setting, since the bolus volume is so small and a rapid response is required, the bolus must be flushed in with, say, 10–20 mls saline, in order to guarantee that the bolus is delivered into the circulation (i.e. so the drug cannot inadvertently remain within the CVP line). Consequently, a drug-free CVP-line must be used, and if any uncertainty exists, then give the bolus (initially at least) into a peripheral vein.

This scenario occurs not infrequently, particularly in patients returning from theatre with their noradrenaline syringe driver on ‘empty’. You then have to sort out the severe hypotension and maintain an adequate blood pressure manually for about 5 mins or so while the nurses set up a new noradrenaline infusion. Fortunately, when a syringe driver alarms and stops there are usually several mls left in the syringe/system which can be used to fill your 1 ml syringe.

Example 3

Postoperative use of noradrenaline in patients with a history of hypertension. A patient with a long history of hypertension requiring quadruple drug antihypertensive therapy, was admitted postoperatively to ITU (following a nephrectomy; preop creatinine 150), with a blood pressure of 110–120 mmHg and poor urine output. From the notes it was clear that her usual blood pressure was approximately 160–170 mmHg, and so a CVP line was inserted and noradrenaline used to push the blood pressure up to 160 mmHg, with the effect that her urine output increased significantly and her creatinine stabilised out at 160–170. The noradrenaline was weaned down over about 4 days (during which her pre-op antihypertensive drugs wore off) by which time her blood pressure stabilised at about 160 mmHg and she was returned to the ward. Her normal antihypertensive therapy was then gradually re-introduced.

References

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⁵Avoid using the existing noradrenaline CVP line, since you need to guarantee that (a) *only* the bolus dose is given, and (b) it is delivered *into* the circulation—you can not flush the bolus with saline down the existing noradrenaline infusion line. Much safer to give it initially via a separate line, until you have control of the blood pressure.

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[Used an infusion of vasopressin 4 U/h, plus two boluses of 0.4 U, in a 83 Kg man relatively refractory to noradrenaline (20 mls/hr of 'single-strength' noradrenaline).]
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8.2 Remifentanyl

Remifentanyl (*Ultiva*) is an ultra short-acting narcotic, used either as a bolus or as an infusion. Remifentanyl pharmacokinetics are not modified by hepatic or renal failure (Absalom and Struys 2006). Duration of action when given as a bolus is approximately 10 mins. See the excellent review by Scott and Perry (2005).

8.2.1 Bolus

Drug	Dilution (in saline)	Bolus dose (adults)
Remifentanyl (Ultiva) 1 mg ampoule	1 mg/20 mls (50 μ g/ml)	0.5–1.5 μ g/kg

Induction of anaesthesia

Remifentanyl is an extremely useful co-induction agent for intubation and for bronchoscopy. It is very cardio-stable and reduces the propofol induction dose by about 50%. Typical co-induction dose for 70 kg adult: 70–100 μ g (in 25–50 μ g increments over 2 mins). Use approximately half the dose in the elderly. Watch out for (a) **respiratory depression**, especially in the elderly (only give during pre-oxygenation), (b) **bradycardia** (have atropine handy), (c) **hypotension**.

During anaesthesia

Bradycardia seems to be most pronounced during anaesthesia with volatiles, so once anaesthesia has been established then titrate initially with 10–20 μ g boluses (70 kg adult) in order to determine the effective dose.

8.2.2 Infusion

For sedation and analgesia in ventilated patients in an ITU setting, the recommendation is to start at about 0.1 μ g/kg/min and titrate by \pm 20% depending on the response, as shown in the following Table.

Drug	Dilution (5% Dex or saline)	Infusion (adults)
Remifentanyl (Ultiva)	$\frac{3 \times \text{kg}}{100}$ mg in 50 mls	start at 10 mls/hr (0.1 μ g/kg/min)

For anaesthesia, any recommendation of specific ranges of MAC to supplement a remifentanyl infusion should really be based on a review of the growing literature of observed MAC reductions (see: Breslin *et al.* 2001, Lang *et al.* 1996, van Delden *et al.* 2002).

For TCI techniques see Absalom and Struys (2007). The Minto 3-compartment model (Minto, Schnider, Egan *et al.* 1997; Minto, Schnider and Shafer 1997) most commonly used for remifentanyl, uses age and lean body mass (LBM) as co-variables, and so requires entry of weight, height and gender as well (Absalom and Struys 2007, p. 16).

- Absalom AR and Struys MMRF (2007). Overview of target controlled infusions and total intravenous anaesthesia. 108 pp. (Academia Press, Ghent, Belgium; <http://www.academiapress.be>) ISBN 978-90-382-11077 [excellent small book sponsored by Cardinal Health, Basingstoke, Hampshire, UK; tel: +44(0)1256-388462]
- Breslin D, Reid JE, Mirakhor RK, Hayes AK and McBrien ME (2001). Sevoflurane-nitrous oxide anaesthesia supplemented with remifentanyl: effect on recovery and cognitive function. *Anaesthesia*; 56, 114–119.

This article attempts to determine the appropriate remifentanyl infusion rate associated with sevoflurane at 1.5, 1.0 and 0.5 MAC. They found that a remifentanyl infusion of 0.34 (range 0.20–0.49 $\mu\text{g}/\text{kg}/\text{min}$) requires a MAC of 0.5 in a population of mean age 30 years and mean BMI 25.1 for operations of mean duration 57 mins.

- Lang E, Kapila A, Shlugman D, Hoke JF, Sebel PS and Glass PSA (1996). Reduction of isoflurane minimal alveolar concentration by remifentanyl. *Anesthesiology*; 85, 721–728. Their conclusion (majority of patients in the age-range 31–55) was that isoflurane (in oxygen only) concentrations of 0.4–0.5 % (i.e., 0.4 MAC₄₀ approx from my charts) required a remifentanyl infusion rate of 0.15–0.3 $\mu\text{g}/\text{kg}/\text{min}$ for adequate anaesthesia (plasma level of 4–8 ng/ml).
- Minto, CF, Schnider TW, Egan TD *et al.* (1997). Influence of age and gender on the pharmacokinetics and pharmacodynamics of remifentanyl. I. Model development. *Anaesthesiology*; 86, 10–23.
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- Scott LJ and Perry CM (2005). Remifentanyl. A review of its use during the induction and maintenance of general anaesthesia. *Drugs*; 65, 1793–1823. [excellent]
- van Delden PG, Houweling PL, Bencini AF, Ephraim EP, Frietman RC, van Niekert J, van Stolk MA, Verheijen R, Wajer OJ, Mulder PGH (2002). Remifentanyl–sevoflurane anaesthesia for laparoscopic cholecystectomy: comparison of three dose regimens. *Anaesthesia*; 57, 212–7.

This article determined the appropriate remifentanyl infusion rate associated with sevoflurane (with no nitrous oxide) at 1.2, 0.8 and 0.4 MAC. They found that a remifentanyl infusion of 0.23 (range 0.12–0.73 $\mu\text{g}/\text{kg}/\text{min}$) requires a MAC of 0.8 in a population of mean age 47 years. Their conclusion was that the optimum combination (for anaesthesia quality and recovery rate) was sevoflurane ET 1.24 % (i.e., MAC₄₇ = 0.7 approx from my charts⁶) and remifentanyl 0.23 $\mu\text{g}/\text{kg}/\text{min}$ (I have converted their $\mu\text{g}/\text{kg}/\text{hr}$ to $\mu\text{g}/\text{kg}/\text{min}$).

⁶See Figures 9.1, 9.2, 9.3.

8.3 Somatostatin analogues & carcinoid

A useful brief overview and references is presented by Mason (2001).

8.3.1 Octreotide

Sandostatin: 1ml ampoule; three concentrations available: 50/100/200 $\mu\text{g/ml}$)

Octreotide is a synthetic analogue of the hypothalamic release-inhibiting hormone somatostatin (BNF), and is a key drug in the management of patients with carcinoid syndrome (Farling and Durairaju 2004; Vaughan and Brunner 1997; Battershill PE and Clissold SP 1989). It is used to counteract serotonin (5HT) and kinin activity and to gain full control of symptoms (subcutaneously: initially 50 μg 1–2 times/day increasing to 200 μg 3 times/day). Octreotide is increasingly being used in the treatment of congenital and postoperative chylothorax (Roehr CC, Jung A, Proquitté H *et al.* 2006).

8.3.2 Ketanserin

Ketanserin is a selective antagonist of anti-5HT₂, the α_1 -adrenoreceptor, and the H₁-histamine receptor (Koopmans *et al.* 2005; Hughes and Hodkinson 1989). Ketanserin reduces portal pressure in animals (Chernow 1988). A 10 mg bolus IV has been used successfully in carcinoid crisis to block mediators (Koopmans *et al.* 2005, Hughes and Hodkinson 1989). Alternatively, ketanserin 10 mg given over 3 mins followed by an infusion of 3 mg/hr is suggested by Mason (2001), Fischler *et al.* (1983), Hughes and Hodkinson (1989).

8.3.3 Carcinoid tumours

Carcinoid (neuroendocrine) tumours have their origin in the endocrine argentaffine cells of the small bowel mucosa, which are part of the so-called APUD family (Amine content, Precursor Uptake, and Decarboxylation). Carcinoid is characterised biochemically by an increased urinary excretion of 5-hydroxyindole-acetic acid (5-HIAA; Mol wt 191), the normal range being 10–47 $\mu\text{Mol/24 hrs}$ (1.9–8.9 mg/24 hrs).

A range of peptides, kinins and prostaglandins can be secreted, including kallikrein, bradykinin, serotonin (5HT), histamine, and substance-P. Less commonly secreted are insulin, ACTH, MSH, gastrin and glucagon. The carcinoid syndrome symptoms of diarrhoea, sedation, hypertension are thought to be due to serotonin; flushing, hypotension and bronchospasm are thought to be due to bradykinin (Mason and Steane 1976).

8.3.4 Anaesthesia for bronchial carcinoid resection

The anaesthetic management of such patients consists primarily of (a) using the drug octreotide for preoperative symptom control (2 days–2 weeks) and also as part of the premedication regimen, (b) avoiding drugs which liberate histamine (e.g., atracurium, morphine), (c) using small boluses of octreotide (10–20 μg) as necessary to counteract symptomatic episodes (flushing, hypotension, bronchospasm). Ketanserin (10 mg bolus IV)⁷ has also been used successfully in carcinoid crisis to block mediators (Koopmans *et al.* 2005, Hughes and Hodkinson 1989). Steroids are often used perioperatively. Bradykinin seems to be the key mediator of hypotension in carcinoid syndrome (Veall *et al.* 1994).

Preoperative control of symptoms: Octreotide is typically given subcutaneously in doses of 50–200 μg 8-hrly.

Premedication: Octreotide 50–100 μg subcutaneously 1 hr preoperatively.

⁷Alternatively ketanserin 10 mg over 3 mins followed by an infusion of 3 mg/hr (Mason 2001).

Induction: Insert the arterial line under local prior to induction. Try to avoid the use of rigid bronchoscopy by the surgeons on induction in order to minimise airway stimulation—suggest they consider flexible bronchoscopy via a single-lumen tube if necessary.

Intra-operatively: Use octreotide intravenously as required to control exacerbations of bronchospasm, hypotension *with* flushing, and bradycardia (100 μ g diluted in 10–20 mls saline). Titrate using small boluses of approximately 10–20 μ g. Note bradycardia associated with heart-block has been reported following a 100 μ g bolus (Dilger *et al.* 2004).

Acute hypertension may be due to serotonin (5HT) (blocked by ketanserin), while acute hypotension may be due to bradykinin (blocked by octreotide). Have a syringe of adrenaline (1/10,000)⁸ immediately available to treat episodes of profound bradycardia or asystolic arrest

Consider including ondansetron (give slowly⁹) for its anti-5HT activity (Wilde and Markham 1996). Consider including chlorpheniramine (anti-H₁), ranitidine (anti-H₂) and aprotinin (anti-kallikrein) (Vaughan, Howard and Brunner 2000, Mason and Steane 1976). Monitor blood glucose (carcinoid tumours may secrete insulin or glucagon). Epidural bupivacaine + fentanyl is fine.

The vasopressors of choice in carcinoid surgery are most probably phenylephrine, metaraminol, and also methoxamine (not currently available), since they are not catecholamines¹⁰ (Koopmans *et al.* 2005). However, I have used a noradrenaline infusion in carcinoid cases on several occasions uneventfully.

Example of intraoperative hypotension

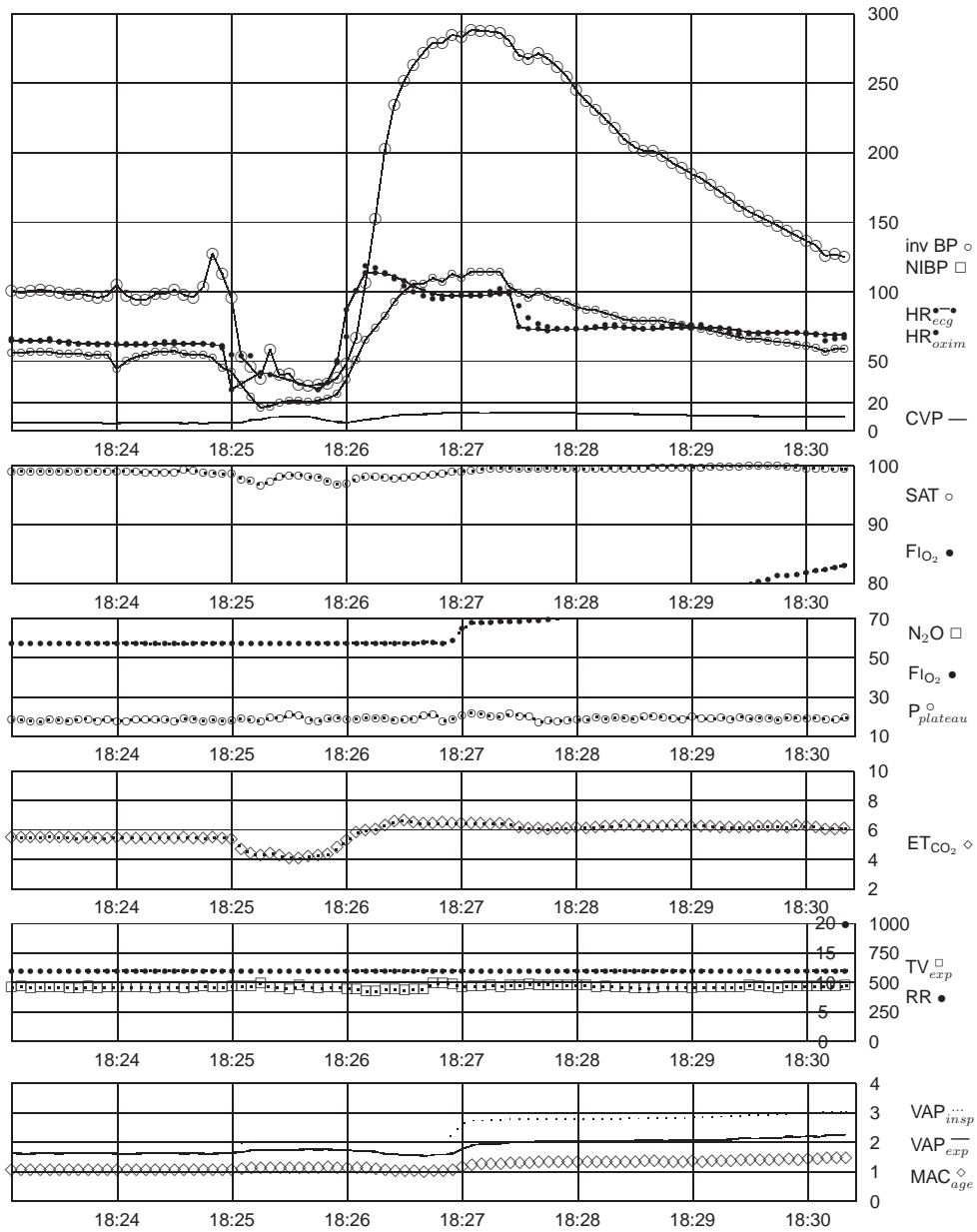
Figure 8.1 shows an episode of extreme hypotension during a thoracic carcinoid resection. During this operation there were two such episodes (one cardiac standstill) which responded rapidly to open cardiac massage, adrenaline (2 ml of 1/10,000) and 20 μ g octreotide via the CVP line. Although a noradrenaline infusion was being used at the time (to counteract the epidural), each of these episodes appeared to be related to surgical manipulation; no noradrenaline boluses were given at any stage.

⁸ 1 mg in 10 mls saline.

⁹ See letter by Cherian and Maguire 2005.

¹⁰ Since *o*-dihydroxybenzine is called *catechol*, sympathomimetic amines having the same OH-substitutions in the benzene ring (i.e., in both the 3- and 4- positions) are termed catecholamines (e.g., dopamine, dobutamine, noradrenaline, adrenaline, isoprenaline).

ANÆSTHESIA RECORD



© RWD Nickalls, S Dales & A Nice 1994–2008: *Xenon5* ANÆSTHESIA RECORD SYSTEM *Linux* \LaTeX 2_ε
 dick@nickalls.org [www.nickalls.org]

Figure 8.1: Anaesthetic record captured by the author’s open-source anaesthesia workstation software *Xenon5* during a thoracic carcinoid resection, showing an episode of bradycardia and extreme hypotension which responded to cardiac massage plus bolus of adrenaline (2 ml 1/10,000) and 20 μ g octreotide—see text. Notice the transient reduction in ET_{CO₂} due to low cardiac output associated with the period of hypotension. The patient made a full and uneventful recovery. (Datex AS/3 monitor; all data points are at 5 sec intervals; BP, NIBP, CVP mmHg; P_{plateau} cm H₂O; TV ml; SAT, F_IO₂, ET_{CO₂}, F_IN₂O, MAC, VAP (sevoflurane) %).

Carcinoid references

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8.4 Haemostatic drugs

See recent review by Mahdy and Webster (2004) discussing the role of agents for reducing perioperative blood loss and transfusion requirements. Consider the cell-saver.

- Bombeli T and Spahn DR (2004). Updates in perioperative coagulation: physiology and management of thromboembolism and haemorrhage *Br. J. Anaesth.*; 93, 275–287. [excellent review article]
- Mahdy AM and Webster NR (2004). Perioperative systemic haemostatic agents. *Br. J. Anaesth.*; 93, 842–858.

8.4.1 Aprotinin

Aprotinin (*Trasylol*) is a protease inhibitor which inactivates free plasmin. It is sometimes useful in cases where significant blood loss from a large oozing tissue surface is anticipated (e.g., in cases where large tumours need to be dissected out, since hyperplasmaemia is sometimes associated with these procedures). However, aprotinin is not without its problems; in 2006 the manufacturers highlighted concerns regarding anaphylaxis (avoid repeat use within 12 months) and nephrotoxicity,¹¹ and more recently it has been associated with excess deaths in coronary artery surgery.¹²

Aprotinin is supplied in 50 ml bottles, the concentration being 10,000 KI Units/ml (Kallikrein Inactivation Units). A typical dose regimen for a 70 kg man (see BNF and discuss with surgeons before anaesthesia) is as follows : 10⁶ Units over 30 mins (to be in just prior to skin incision), followed by a maintenance regimen of approximately 10⁶ Units/hr during the operation.

8.4.2 Recombinant factor VIIa

- Ahonen J and Jokela R (2005). Recombinant factor VIIa for life-threatening postpartum haemorrhage. *Br. J. Anaesth.*; 94, 592–595.
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¹¹<http://www.fda.gov/medwatch/safety/2006/safety06.html>

¹²*British Medical Journal* (2007); 334, 336–337