Pain Control in the Last 48 Hours

- It is believed that 40% of patients may have an exacerbation of pain during the terminal phase.

- In the last 48 hours, the syringe driver must be employed. The dose of diamorphine to infuse depends upon current opioid requirements. A table of conversion factors is shown on page 7. Unresolved somatic pain can be a cause of terminal agitation.

- If the patient was previously taking slow release (SR) morphine or hydromorphone, the driver should be started at the time the next dose was due. There is no need for a crossover period; the syringe driver can be started at the time of the next oral SR opioid dose. However, other practitioners recommend starting the driver 4 hours before the next oral SR opioid dose is due. In both cases, to achieve or maintain adequate symptom control, it may be necessary to administer suitable subcutaneous stat. doses.

- If a patient is currently using a fentanyl patch, it is wise to continue with this, but ensure that 'rescue' analgesia is given for breakthrough pain with subcutaneous diamorphine. The total daily rescue medication can then be given as diamorphine via a syringe driver. In general:

  25µg/hr patch = 30mg diamorphine (in 24 hours) = 5mg 'rescue' dose
  100µg/hr patch = 120mg diamorphine (in 24 hours) = 20mg 'rescue' dose

Resistant Cases

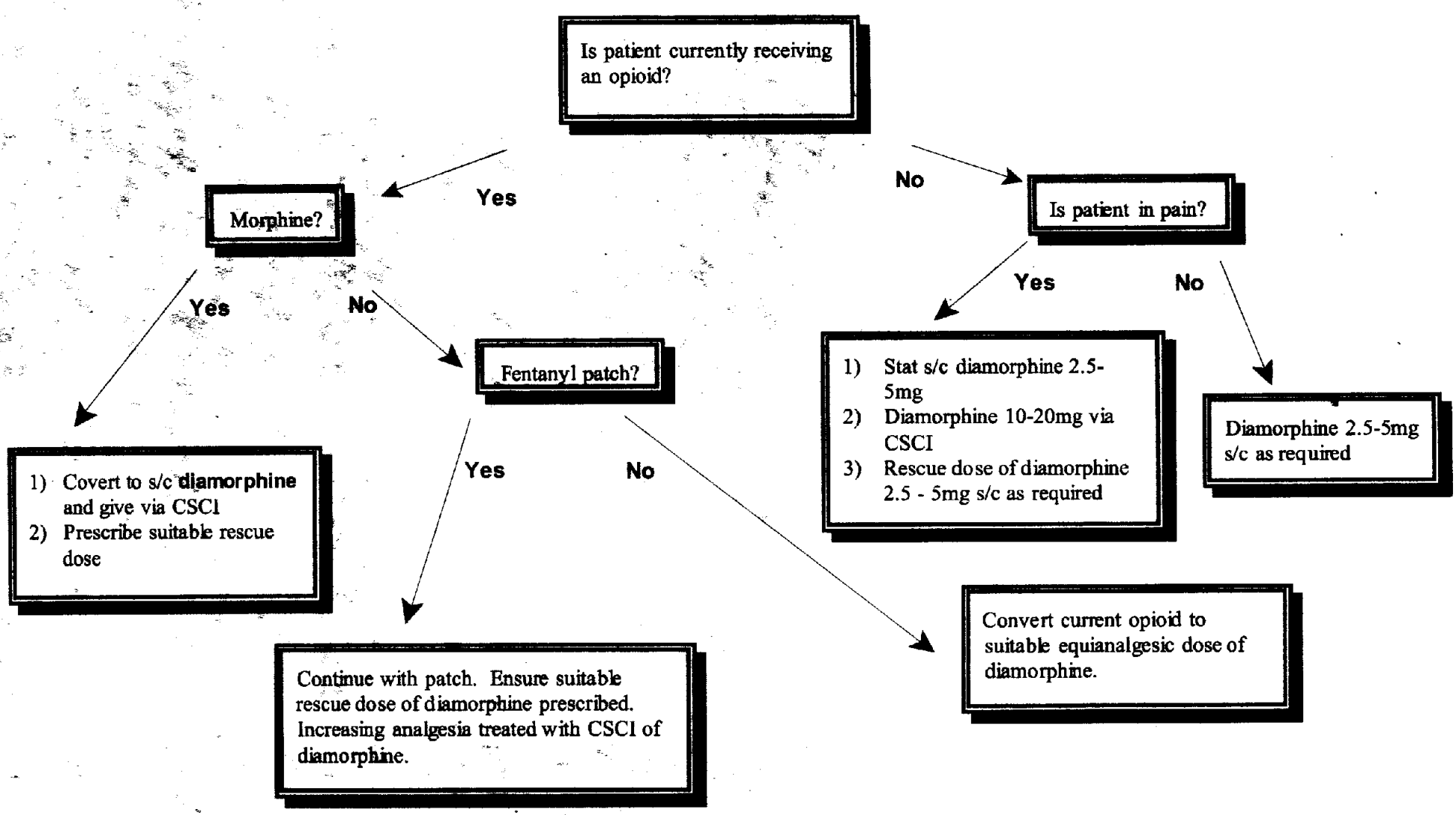
- If the patient shows signs of incident pain (ie agitation / pain on movement) this is ***not*** an indication to increase 24 hourly analgesia. Administer a 'rescue' dose of analgesia coupled with a 5-10mg subcutaneous dose of midazolam ***at least 30 minutes prior*** to movement. Do ***not*** increase daily analgesia dose as a result.

- If the patient was being treated for neuropathic pain before entering the terminal phase, ensure clonazepam 2 - 4mg is added to the syringe driver. The dose may need to be increased as necessary, up to 8mg. Do not then add midazolam to the driver for terminal agitation because clonazepam will be effective in treating this.

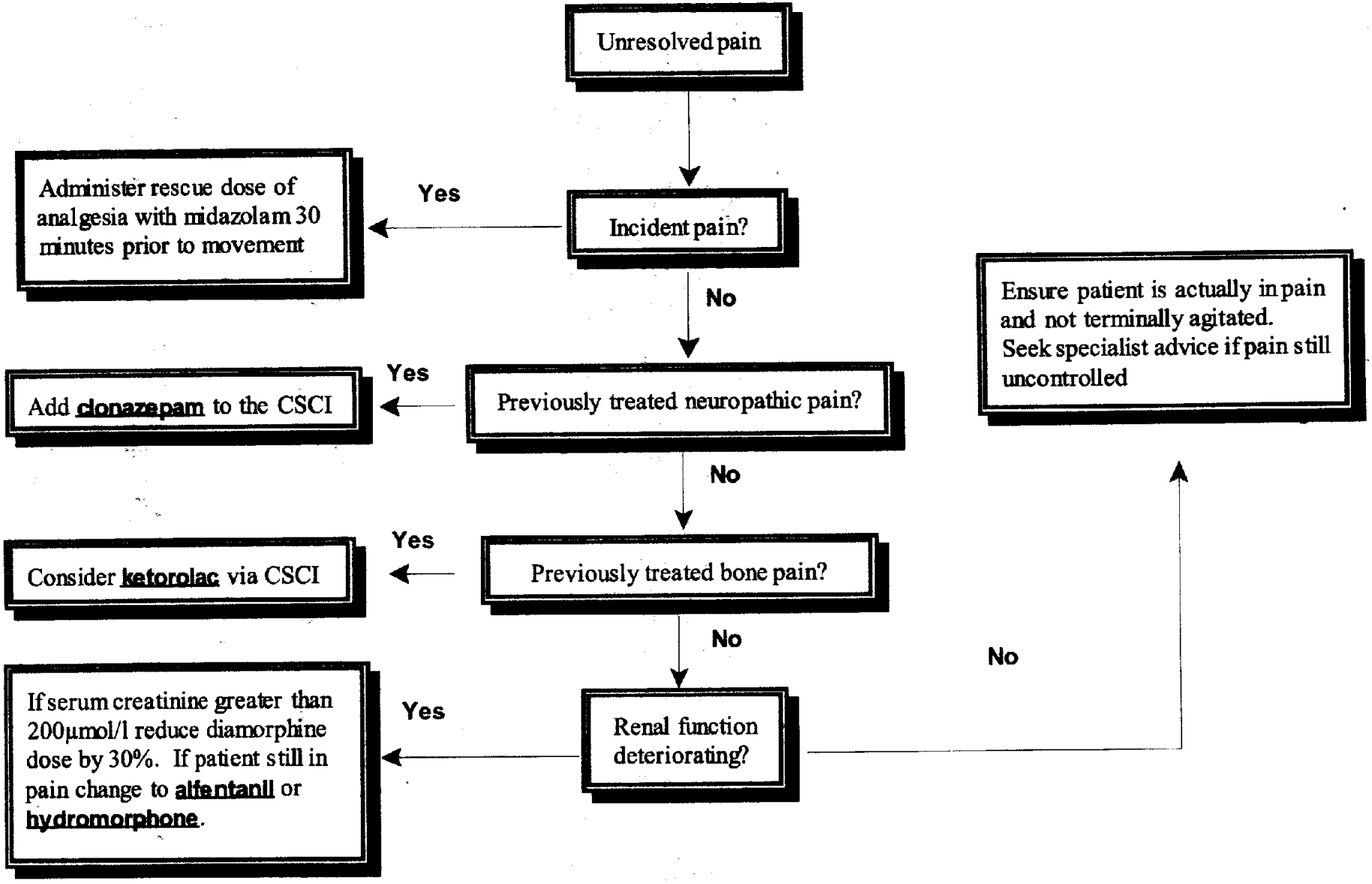
- Renal failure can precipitate diamorphine / morphine toxicity due to the accumulation of the metabolite morphine-6-glucuronide. If serum creatinine is greater than 200µmol/l, then the diamorphine (or morphine) dose should be reduced by 30%. If the patient is not pain controlled after this dose reduction, change to alfentanil (see page 10 for guidance on the use of alfentanil).

- If the patient was previously being treated for bone pain before entering the terminal phase, the use of a NSAID (eg ketorolac) should be considered. This will more than likely necessitate the use of a second syringe driver.

Control of Pain in the Last 48 Hours



Control of Resistant Pain in the Last 48 Hours



Overview of Nausea and Vomiting

Introduction

- Vomiting is considered to be a protective mechanism in that potentially toxic substances are forcefully ejected. This is believed to have developed during evolution because of its protective value. However, the basis for vomiting that occurs in pregnancy or motion sickness remains unclear.

- Nausea usually precedes vomiting and can be described as an unpleasant sensation associated with the urge to vomit. It causes gastric stasis, so an initial parenteral dose of an anti-emetic will be necessary.

- The complex act of vomiting is controlled by the vomiting centre, which is located in the reticular formation of the lower medulla. Stimulation of the vomiting centre by impulses from the ***chemoreceptor trigger zone*** (CTZ), ***pharynx and gastrointestinal tract*** (via vagal and somatic afferents), ***vestibular apparatus*** and higher centres of the ***brain*** (eg visual cortex) results in emesis.

- About 50-60% of patients with advanced cancer will suffer from nausea and vomiting.

Neuropharmacology

- It is important to have an understanding of the main neurotransmitters involved in the emetic process (see figure 1) to ensure optimum pharmacological intervention.

- The ***CTZ*** is found in the area postrema and lies 'outside' the blood-brain barrier. It is stimulated by emetic substances received through the blood as well as the CSF. Dopamine (D_2), opioid, serotonin (5-HT_3) and muscarinic (ACh_m) receptors have been located here, although the principal emetic pathway appears to be dopaminergic. The ***nucleus tractus solitarius*** is the main site for peripheral input from vagal and afferent neurons. Dopamine (D_2), histamine (H_1), serotonin (5-HT_3) and ACh_m receptors are found here. Impulses from the ***vestibular apparatus*** pass through the vestibular nucleus (where H_1 and ACh_m receptors are found) to the vomiting centre, via the cerebellum. Receptors found within the ***vomiting centre*** include D_2, H_1, 5-HT_2, ACh_m and μ-opioid.

Causes

- The cause(s) of nausea and vomiting must be determined to enable the most suitable choice of anti-emetic. Some of the common causes of nausea and vomiting encountered in palliative care are shown in box below.

  - Drugs (eg opioids, cytotoxics, carbamazepine, digoxin, iron, NSAIDs)
  - Gastroparesis
  - Gastric ulceration
  - Bowel obstruction
  - Bowel colic
  - Constipation?
  - Renal failure
  - Hypercalcaemia
  - Raised intracranial pressure
  - Anxiety
  - Infection
  - Radiotherapy

Figure 1 - Summary of receptor types and stimuli in the vomiting response

CHEMORECEPTOR TRIGGER ZONE

eg drugs
uraemia
hypercalcaemia

GUT MUCOSA
(via vagal/somatic afferents)

eg GI obstruction
Bowel colic
Tumour mass
Constipation??

VESTIBULAR APPARATUS

(Shaded boxes represent prominent pharmacological target)

Further Management

a) **Correct Reversible Causes**

❑ Hypercalcaemia	Rehydration ± pamidronate
❑ Raised intracranial pressure	Dexamethasone
❑ Gastritis	Misoprostol (low dose initially), or Nizatidine, or Lansoprazole
❑ Constipation	Laxatives (although problem may persist)

b) **Non-Drug Measures**

- ❑ Avoidance of smell of food and unpleasant odours
- ❑ Calm, relaxing environment
- ❑ If persistent nausea, try regular small meals, cold foods. Avoid fatty foods

c) **Anti-Emetics**

- ❑ The choice of anti-emetic will depend on the cause(s) of nausea and vomiting. Most patients, however, have multiple and irreversible causes.
- ❑ Figure 2 illustrates the areas of the vomiting pathway that certain drugs act.
- ❑ Anti-emetics may act at more than one type of receptor in producing their effect. For example, cyclizine may interact at both muscarinic (ACh_m) and histamine (H_1) receptors; metoclopramide acts at dopamine (D_2) and serotonin (5-HT_3) (at high doses) receptors, an action that could contribute to its efficacy in controlling nausea and vomiting associated with cytotoxic agents.
- ❑ No currently available drug will antagonize ***all*** receptor sites involved in the vomiting response. Neither is there a universal agent that will block the final common pathway, the output from the vomiting centre. Consequently, a combination of agents may have a greater anti-emetic action than a single drug.

- ❑ For resistant cases of nausea and vomiting, the following table should facilitate the choice of a suitable anti-emetic.

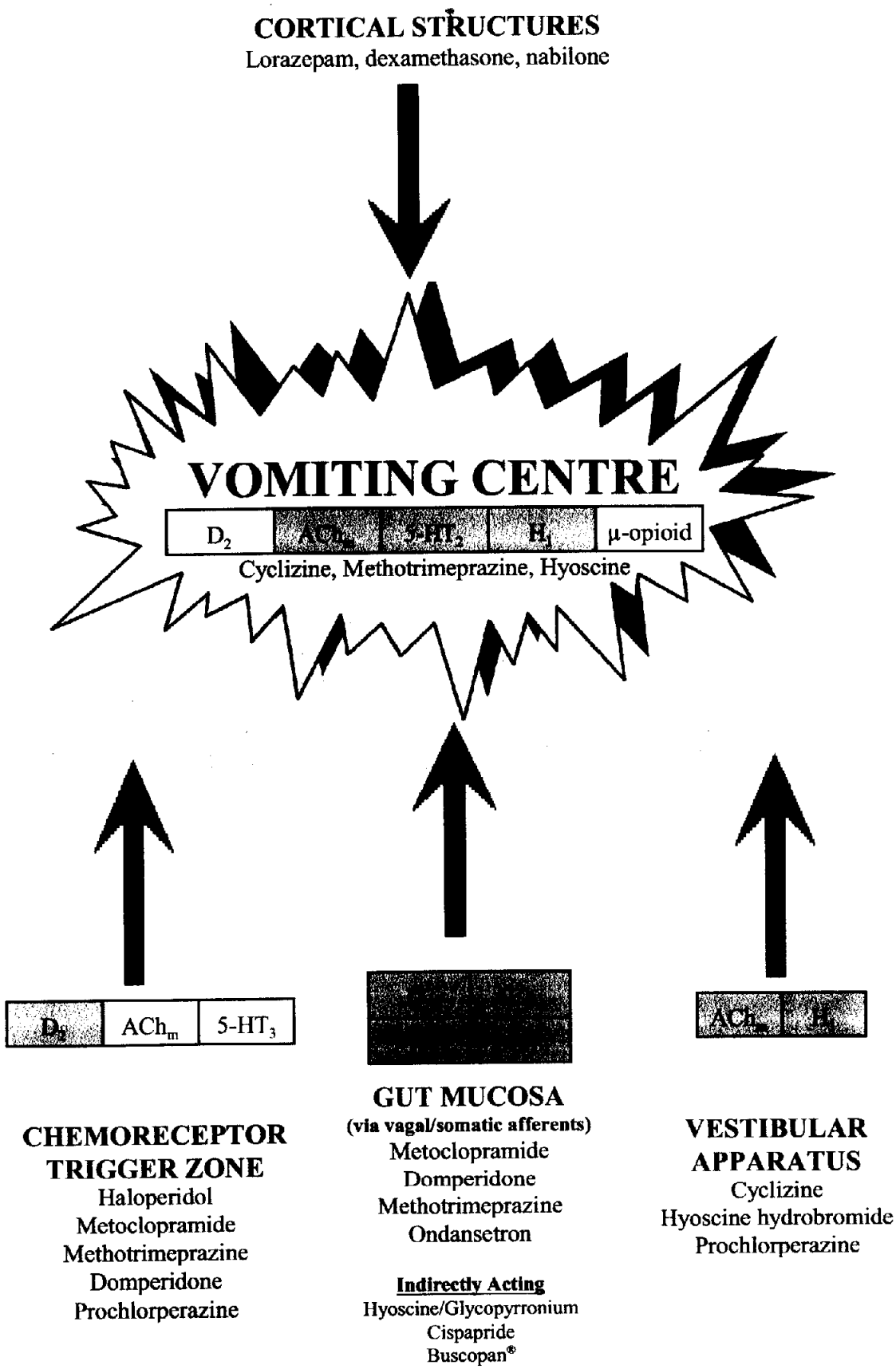
- ❑ However, in general:

  - ◆ methotrimeprazine 6.25 - 12.5mg by s/c injection at night is usually considered to be the most effective treatment in resistant cases,

  - ◆ if large volumes are being vomited, the addition to the syringe driver of octreotide 300µg and glycopyrronium 1.2mg can be considered.

  - ◆ NB - The 5-HT_3 antagonists are unlikely to be of benefit unless the cause of nausea/vomiting is due to damage of GI enterochromaffin cells - ie recent radiotherapy/chemotherapy, or tumour infiltration.

Figure 2 - Summary of drug action in the vomiting response



Nausea and Vomiting in Palliative Care - Causes and Suggested Treatment

Cause	1st Line Drug	Stat Dose[1]	Daily Dose[1]	2nd Line Drug[2]	Stat Dose[1]	Daily dose[1]	Notes
Gastric stasis	***Metoclopramide***	10-20mg (sc, po, iv)	30-120mg (sc, po, iv)	***Domperidone***	10-20mg (po) 30-60mg (pr)	40-80mg (po) 120-240mg (pr)	Anticholinergic drugs antagonise the effects of prokinetic drugs.
Gastric irritation (eg drugs, tumour infiltration)	***Metoclopramide***	10-20mg (sc, po, iv)	30-120mg (sc, po, iv)	***Methotrimeprazine***[3] or ***Ondansetron***[4]	6.25mg (sc) 12.5mg (po) 8mg	6.25-25mg(sc) 12.5-50mg(po)	Consider ***misoprostol*** or ***omeprazole / lansoprazole*** if NSAID induced.
Total bowel obstruction with colic	***Haloperidol*** and consider ***Buscopan®*** ***or*** ***Glycopyrronium*** (for colic and may reduce volume of vomit)	5mg (po,sc) 20mg (sc,po) 400µg (sc)	5-10mg (po,sc) 80-160mg (sc,po) 800-1600µg (sc)	***Add cyclizine*** ***Methotrimeprazine***[3]	50mg (sc, po, iv) 6.25mg (sc) 12.5mg (po)	100-150mg (sc, po, iv) 6.25-25mg(sc) 12.5-50mg(po)	In difficult cases, consider the use of ***dexamethasone***[5] 8-12mg daily (po,sc). ***Octreotide*** 300-600µg daily (sc) with ***glycopyrronium*** *may* be beneficial if large volume vomit.
Partial bowel obstruction without colic	***Metoclopramide*** or ***Domperidone***	10-20mg (sc, po, iv) 10-20mg (po) 30-60mg (pr)	30-120mg (sc, po, iv) 40-80mg (po) 120-240mg (pr)	***Add dexamethasone***	8-12mg (po,sc)	8-12mg (po,sc)	Consider faecal softner (eg ***magnesium hydroxide*** 10ml bd, or ***docusate*** 200mg bd, arachis oil enema).
Chemoreceptor trigger zone (eg drugs, hypercalcaemia)	***Haloperidol*** or ***Cyclizine***	1.5-5mg (sc,po) 50mg (sc, po, iv)	1.5-10mg (po,sc) 100-150mg (sc, po, iv)	***Methotrimeprazine***[3] or Combination of ***haloperidol*** *and* ***cyclizine***	6.25mg (sc) 12.5mg (po)	6.25-25mg(sc) 12.5-50mg(po)	
Raised intracranial pressure	***Dexamethasone*** and ***Cyclizine***	8-16mg(sc,po)	8-16mg(sc,po) 100-150mg (sc,po,iv)	***Hyoscine hydrobromide*** or ***Methotrimeprazine***[3]	400µg (sc) 6.25mg (sc) 12.5mg (po)	800-1600µg (sc) 6.25-25mg(sc) 12.5-50mg(po)	

1) Subcutaneous and oral routes are preferable - intramuscular should be avoided.
2) Substitute the 1st line drug with the 2nd line agent ***unless*** the table states otherwise.
3) Very broad spectrum anti-emetic with few adverse effects at the low dose used. Main problems are sedation and postural hypotension. Dose can be given once daily, preferably at night. Injection site reactions can be reduced by mixing with saline 0.9% rather than water.
4) Useful if problem due to cellular damage with subsequent 5-HT release eg radiotherapy, renal failure
5) Once daily sc injection preferable rather than infusion, especially due to compatibility problems.

Terminal Restlessness

General Points

- Terminal restlessness is defined as:

  > "agitated delirium in a dying patient, frequently associated with impaired consciousness and myoclonic events."

- Patients can suffer symptoms of agitation, moaning/crying out, physical restlessness, myoclonic spasms, or convulsions.

- Its presence can be distressing for both family and carer and may leave unpleasant, negative memories of an otherwise fairly peaceful dying process.

- The cause of terminal restlessness can be multifactorial; several causes are shown in the box below.

- For patients close to death (ie the last 48 hours) it is generally inappropriate to investigate and treat metabolic or infective causes.

- However, other causes can be considered to be 'reversible' (underlined in the box below) and these should be managed accordingly. If the patient is ***not*** close to death, ***all*** identified causes should be treated.

  - drugs (eg opioids, anticholinergic agents, carbamazepine,)
    (note that previously tolerated doses of drugs may become toxic as the disease progresses, or renal/liver function deteriorates.)
  - pain,
  - brain tumour / metastases
  - hypercalcaemia / hyponatraemia / hypoglycaemia,
  - renal failure/liver failure
  - constipation,
  - urinary retention,
  - infection,
  - nicotine / alcohol withdrawal and
  - emotional distress (eg fear, anxiety).

Further Management

1) Check to see if a 'reversible' cause as outlined above can be identified and treat accordingly.

   eg if patient has suddenly stopped smoking, consider the use of a nicotine patch.

2) Ensure stat. doses of midazolam are prescribed for breakthrough agitation.

3) For more resistant forms of terminal restlessness, the following is suggested, in order:

   i) If previous neuropathic pain, change midazolam to clonazepam 4mg (use 2mg if less than 30mg midazolam in 24 hours). The dose may need to be increased as necessary, up to 8mg. Continue with midazolam for stat doses.

ii) Add methotrimeprazine 25mg to the driver (check for compatibility). The dose can be increased as necessary (usually in 25 - 50mg increments, depending on severity) up to a max of 200mg. This drug is reserved as a 2nd line agent because of the potential for myoclonus. It is a useful adjunct to a benzodiazepine for uncontrolled agitation.

iii) In the event that the above measures fail to control symptoms, change to phenobarbitone 200mg s/c over 24 hours. This must be given via a separate driver. The dose can be increased if necessary to 600mg.

Respiratory Tract Secretions

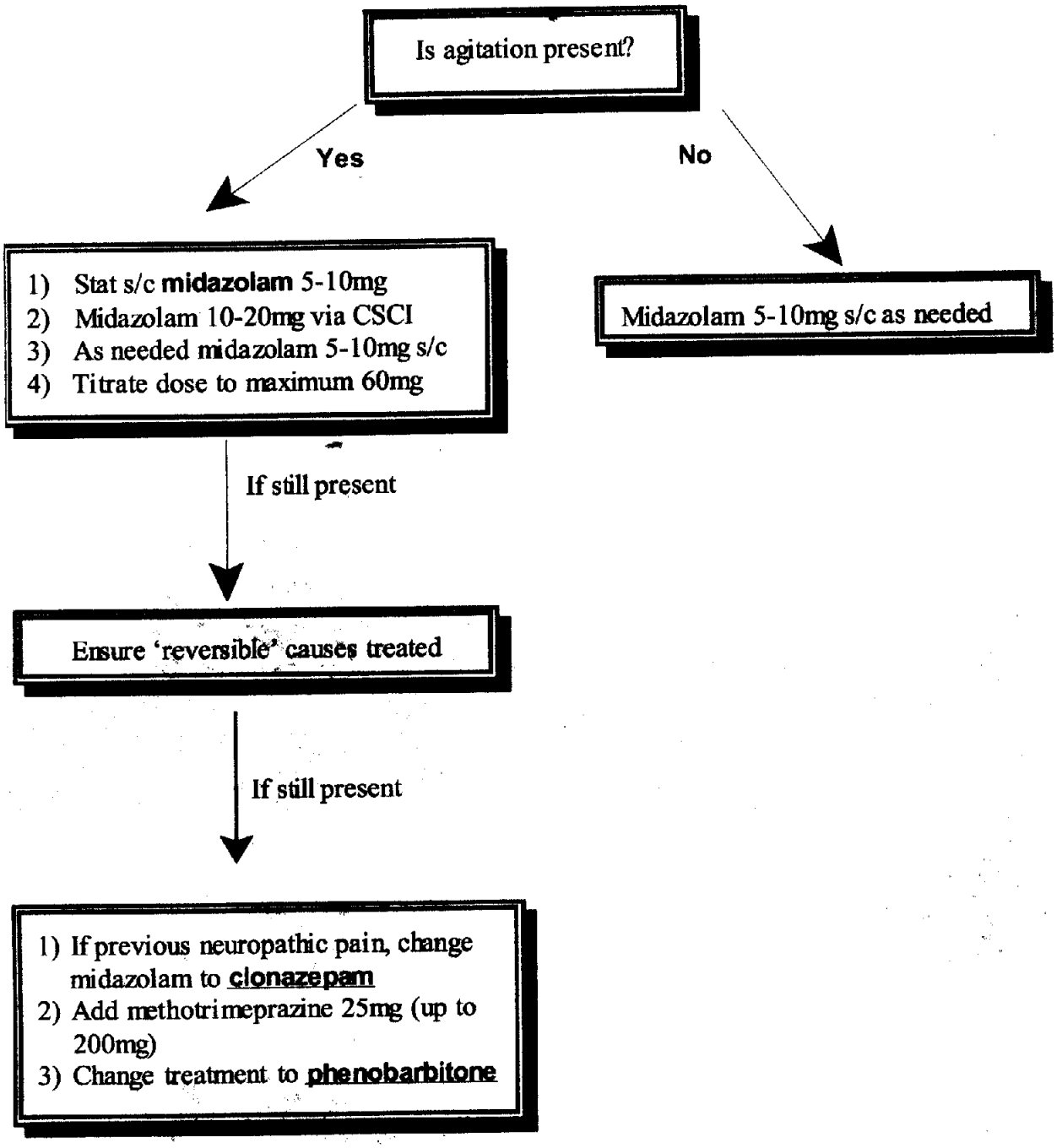
- Drugs will not be able to 'dry-up' secretions already present, so it is important that treatment is initiated as soon as possible, preferably before symptoms appear.

- The 'death rattle' is usually more disturbing for relatives and carers than the patient, who is usually semi-conscious.

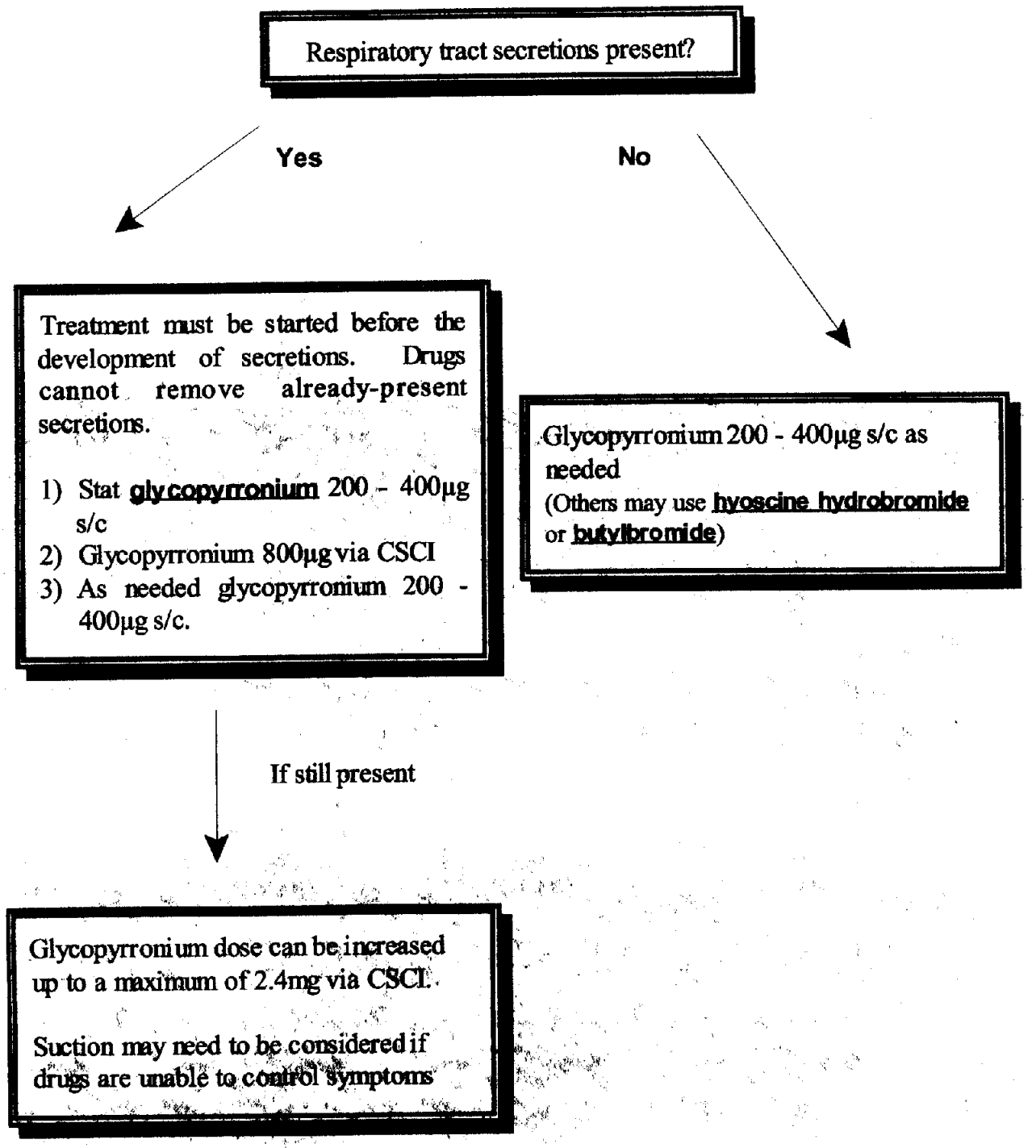
- The recommended treatment is glycopyrronium 0.8 - 2.4mg over 24 hours via the syringe driver. Ensure stat. doses are prescribed for breakthrough secretions. Other centres use Buscopan® (cheaper than glycopyrronium, but not as effective) and hyoscine hydrobromide (more expensive and no more effective than glycopyrronium).

- Volume is likely to be the main problem encountered with the treatment of this condition. If the patient has not responded to 1.6mg of glycopyrronium, 2.4mg is recommended. This equates to 12ml of liquid. The Graseby MS26 can infuse a maximum of 20ml (using a 30ml syringe). It is possible that the total volume to be infused will exceed this amount. In such cases, a 12 hourly infusion rate will be needed.

Control of Terminal Agitation in the Last 48 Hours



Control of Respiratory Tract Secretions in the Last 48 Hours



Appendix I

Syringe Driver Chart and Record Sheet

Name:

Ward:

Syringe Driver - Nursing Administration Record

All syringe drivers should be checked 4 hourly to ensure site viability, correct delivery and to ensure no crystallisation or precipitation has occurred. Nurses should sign below when the driver is started, and every time it is checked. Any problems, such as resiting, should be recorded. Inform the doctor or pharmacist if crystallisation or precipitation occurs.

Date	Sign	Dose(s)	Time Started	0200	0600	1000	1400	1800	2200	Comments