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High-risk medication alert for vincristine injection

Appendix 3: Literature review

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1. Summary and key messages

An extensive review of published literature and other data associated with the inadvertent intrathecal injection of vincristine was undertaken to inform the development of the alert and the recommendations for risk-reduction.

The aims of the literature search were to:

- review cases of this medication error and the contributing factors,
- determine risk reduction strategies that have been recommended and data on their uptake, and;
- review the applicability of these strategies to develop recommendations for the Australian setting and national dissemination via the alert notice.

The review sources included the international medical, pharmaceutical and nursing literature; Australian incident reporting systems, adverse drug reaction and coroners' databases; and websites of international medication and patient safety organisations. Personal contact with health professionals involved with developing safe systems for vincristine was sought to follow up on recent activities.

The main findings of the literature review are summarised below.

1.1. Case reports of inadvertent intrathecal administration of vincristine

Fifty-five cases were found to have been reported since the first case in 1968⁽²⁾. The most recent report was published in November 2005 and detailed the death of a young Californian man^(73,74). A summary of the detailed information published for thirty-three of these cases is included in the literature review, specific details for the other twenty-two cases were not available.

There have been three cases reported in Australia, one in Adelaide in 1986⁽⁵¹⁾, one in Geelong in 1995⁽⁶⁵⁾ and the most recent case in Sydney in 2003^(27,28). In two of the cases there was a fatal outcome and one resulted in permanent quadriplegia⁽⁶⁵⁾.

In 85% of cases the outcome was fatal with devastating neurological effects in the few survivors. Adults and children were found to be at risk, with 50% of cases reported in each group. Many of the cases involved patients in remission or with curable disease.

In the majority of reported cases, the error was recognised immediately, usually within minutes of the injection. Treatment approaches reported were typically very aggressive involving attempts at removal or dilution of the vincristine and administration of agents to counteract its neurotoxic effects. There have not been consistently good results following any of the treatments and implementation of preventative strategies is critical.

1.2. Contributing factors

A number of key contributing factors were identified:

- The most common contributing factor is prescription of intravenous vincristine to be given at the same time or on the same day as doses of cytotoxic medications to be given intrathecally.
- Storage and transport of intravenous and intrathecal medications together.
- Product presentation specifically "look alike syringes" and inadequate labelling.
- Staff factors predominantly the level of experience and knowledge of chemotherapy and of local practices.
- Procedural issues including delegation of authority and checking procedures.

1.3. Recommendations for prevention

Given the almost invariably fatal outcome of this error, despite aggressive treatment, prevention is of the utmost importance and a number of the case reports provided recommendations for reducing the

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risk of recurrence. Even the early reports suggested approaches aimed at **reducing system error** and making it harder for, well intentioned but fallible, humans to make mistakes.

Published recommendations for reducing the risks of inadvertent intrathecal vincristine administration were identified from medication/patient safety, professional and regulatory organisations from Australia, the United Kingdom, Canada and the United States of America.

The table below summarises the current key recommendations made by country.

| Recommendation | Australia | UK | USA | Canada |
|---|-----------|--|-----|--------|
| Only specifically trained and designated oncology staff should prescribe, prepare, dispense and administer cytotoxic medication. | ✓ | ✓ | | |
| Medical staff must use a formal checking procedure, involving an oncology trained nurse, to ensure that the right drug is given at the right dose, by the right route, by the right method, to the right patient. | ✓ | ✓ | ✓ | ✓ |
| Patients or their families may be involved in the checking process. | | ✓ | ✓ | ✓ |
| Intrathecal chemotherapy should only be administered in an area where no other cytotoxic drugs are available. | ✓ | ✓ | ✓ | ✓ |
| Use specifically designated containers both for transportation of intrathecal drugs from the pharmacy and for storage on the ward. | ✓ | ✓ | ✓ | ✓ |
| Intrathecal doses must be delivered separately and preferably administered after other drugs to be given by other routes are supplied to the ward and administered. | ✓ | ✓ | ✓ | ✓ |
| All intrathecal drugs must be packaged separately and clearly labelled both on the syringe and on the outer container 'For Intrathecal Use' | ✓ | ✓ | ✓ | ✓ |
| Vincristine should be clearly labelled both on the syringe and on the outer container "For Intravenous Use Only – Fatal If Given By Other Routes'. Negative labels, such as 'Not for Intrathecal Use' must never be used. | ✓ | ✓ | | |
| Vincristine should be prepared in a small-volume intravenous bag rather than a syringe. | ✓ | Recommended after feasibility review. Not currently in place | ✓ | ✓ |

| Recommendation | Australia | UK | USA | Canada |
|--|-----------|----|-----|--------|
| Consideration should be given to developing novel methods for spinal drug delivery. As a matter of design safety, standard intravenous syringes should not be able to be used for spinal administration. | ✓ | ✓ | | ✓ |

1.4. Equipment and design solutions

A design solution that would address potential mis-connection error would reduce the reliance on the various recommended human factors approaches and potentially totally eliminate the risk of inadvertent intrathecal injection. **The optimal approach would be modification of existing equipment whereby syringes for intravenous use and spinal connectors are incompatible.**

This approach has also been recommended in prevention of mis-connection error with oxygen and medical gases ⁽⁷⁶⁾. Of course eliminating the potential for connection error with medications does not remove all sources of potential error. An error may still occur during the manufacturing process for example if the wrong syringe is inadvertently used or the incorrect medication is drawn up.

Prototypes of new connectors/syringes have thus far been found not to be commercially viable.

Note: As the optimum design solution is currently not available the vincristine alert focuses on preventing errors through achievable design solutions.

1.5. Key messages

The key messages from the literature review performed for vincristine were that:

- the catastrophic outcome of inadvertent intrathecal administration of vincristine is irreversible and usually fatal;
- both children and adults are at risk;
- the only way to prevent this error is to “design out” the potential for it to occur i.e. make it **physically impossible** to connect the vincristine injection to a spinal needle;
- there is a solution which is safe and is currently being used in Australia and the USA. It requires no additional equipment, is relatively low cost and achievable; and
- due to the potential, irreversible and fatal outcomes, the risk of vincristine given intrathecally far out weighs the potential vesicant risks of using diluted solutions.

2. Methodology

A review of National and international literature and data associated with the inadvertent intrathecal injection of vincristine was undertaken. The aims were to:

- review cases of this medication error and the contributing factors,
- determine recommended risk reduction strategies that have been used, and;
- discuss the applicability of these strategies to develop recommendations for national dissemination via the alert notice.

The literature review involved searching the following domains:

- Medline, Embase, Reactions
- Australian Incident Monitoring System (AIMS);
- Australian Adverse Drug Reaction Advisory Committee database; and
- National Coroner's Information System
- overseas medication safety websites including www.ismp.org, www.jcaho.org, www.ismp-canada.org, and www.npsa.nhs.uk;

The data from the literature review was considered by the Steering Committee for the project in consultation with key stakeholders.

3. Background

Medication errors involving inadvertent intrathecal injection of vincristine have been reported repeatedly overseas and in Australia. In the vast majority of cases this error results in a fatal outcome for the patient. All result in life changing and tragic effects on the families and on the hospital staff involved⁽¹⁾.

These tragic errors continue to occur despite repeated warnings over many years and despite promulgation of risk-reduction strategies and in some cases, standards. These errors are rare, catastrophic and very preventable.

Not again!

“Again a young patient with leukaemia is dying, not from his disease, but from an erroneous intrathecal injection of vincristine, intended for intravenous use. Again, the newspapers express outrage...the hospital apologises, again ...two doctors are suspended...and steps will be taken, again. How could this happen, again?”⁽³⁷⁾

Vincristine, a vinca alkaloid, is a naturally occurring chemical obtained from the periwinkle plant. It has been used as a cytotoxic medicine for over forty years and is effective in a range of haematological malignancies and solid tumours in both paediatric and adult settings. It is commonly used in combination with other cytotoxic agents for treatment of acute lymphoblastic leukaemia, non-Hodgkin's lymphoma, myeloma, Wilm's tumour, Ewing's sarcoma and some brain tumours. The other vinca alkaloids, vinblastine, vinorelbine and vindesine, are also used in the management of various malignancies.

All the vinca alkaloids must only be administered intravenously. They are classified as vesicant drugs, that is, they have the potential to cause local tissue injury and necrosis if extravasation occurs (leakage of an intravenously administered medicine from a vein into the surrounding tissue)⁽⁷⁵⁾. Vincristine extravasations typically cause pain, erythema and localised swelling within minutes. Blisters in the skin appear over the subsequent days and resolve slowly over several weeks. Fortunately, most extravasations from vinca alkaloids do not produce frank skin ulceration⁽⁷²⁾. The extent of tissue injury is reduced by use of subcutaneous injections of hyaluronidase and warm compresses⁽⁷⁸⁾.

Extravasation of cytotoxic agents rarely occurs when proper techniques are followed^(54,72). Whilst the incidence of extravasation associated with use of vincristine (or other vinca alkaloids) has not been widely studied, a recent survey of Australian hospitals showed rates of vincristine extravasation of 0.03 – 0.041% in adults and 0.059% in paediatric practice⁽⁷²⁾. An Australian database recording extravasations and their treatment received 162 reports, none of which involved vincristine⁽⁶⁷⁾.

The major dose-limiting side effect of vincristine in therapeutic use is peripheral neurotoxicity. This is manifest predominantly as a mixed sensory motor neuropathy characterised by symmetrical distribution of signs and symptoms and is largely reversible following cessation of treatment. Effects on the autonomic system and cranial nerves may also occur. The neurotoxic effects are the result of interference with microtubule function resulting in blocked axonal transport and subsequent degeneration. Central nervous system toxicity following intravenous administration is rare and limited by the poor penetration of the blood brain barrier.

The characteristic clinical course, which follows intrathecal administration of vincristine, is a slow and painful paralysis reflective of the progressive, ascending myeloencephalopathy that occurs. First signs are often meningism with lower limb or back pain followed by lower limb weakness, urinary retention (or frequency), absent reflexes and gradual loss of nerve and muscle function, culminating in respiratory failure and brain stem death.

4. Case reports

4.1. Summary

The first case report of accidental intrathecal injection of vincristine was published in 1968⁽²⁾. This case involved a two and a half year old girl with acute lymphocytic leukemia (ALL) being treated with a number of cytotoxic medications including intrathecal methotrexate and intravenous vincristine. She had been diagnosed for 15 months, and following treatment experienced two episodes of remission, when 3mg of vincristine was accidentally administered into her spine. Despite an attempt to remove the vincristine via exchange of her cerebrospinal fluid (CSF) with saline, the little girl experienced catastrophic neurological toxicity. On the second day she developed opisthotonic posture and thrashing movements. On the third day respiratory paralysis occurred and she became comatose and died.

Since this report, a further 31 similar cases have been documented in the literature^{3-22, 27,31,51,65, 68,73,74}. These reports are summarised in Appendix 4.

A number of the reports have only been documented via the lay press^(27,51,65,73,73), legal news items⁽²²⁻²⁵⁾, in editorials⁽²⁸⁾, in medication alerts^(18,31,74,77) or via letters from pharmaceutical companies⁽⁹⁾.

Many of the reported cases have occurred in the United Kingdom (UK). The National Patient Safety Agency reports fourteen cases between 1975 and 2001⁽²⁹⁾.

There have been three cases reported in Australia, one in Adelaide in 1986⁽⁵¹⁾, one in Geelong in 1995⁽⁶⁵⁾ and the most recent case in Sydney in 2003^(27,28). Two were fatal and one resulted in permanent quadriplegia⁽⁶⁵⁾.

Of the 32 reported cases associated with vincristine, it can be confirmed that at least 16 (50%) occurred in children or teenagers and, in 11 (69%) of these, the patients were 10 years old or younger. All patients were being treated for either leukaemia; most commonly ALL, or lymphoma and many were in remission or had curable disease. Two cases involved intraventricular administration via an Ommaya reservoir^(13, 15).

An assessment of the true incidence of inadvertent intrathecal injection of vincristine is not possible as there are numerous cases referred to which have not been published in the international medical literature^(5, 23,27, 29, 30, 45,68) and it is likely that there are many more which have not been documented further than the institutional level. One independent review in the USA identified 54 cases since 1968^(45,66). Another case occurred subsequent to this in California in late 2005^(73,74).

Accidental intrathecal administration instead of intravenous administration has also been reported with other chemotherapeutic agents, including the vinca alkaloids, vindesine and vinblastine⁽⁶⁸⁾ and anthracyclines, daunorubicin⁽⁷⁰⁾ and doxorubicin⁽⁶⁹⁾. In a number of these cases, vincristine was also part of the treatment regimen and was appropriately given intravenously.

Whilst most of the errors were recognised within minutes or hours and, many involved aggressive attempts at treatment, death followed within days to weeks in all but five cases (84%). One patient⁽⁹⁾, had minimal lower extremity neuropathy however succumbed to their primary disease after three months. Those who survived extended periods were left with severe neurological complications including quadriplegia and paraplegia^(13, 15, 19, 65). In another case⁽¹¹⁾, the patient was noted to be brain dead 29 days after the injection, however was sustained with supportive care for a long period until this was withdrawn and death occurred due to the primary disease on day 348 (For this review, this patient is considered a fatality).

Salient points

- Three cases of accidental administration of vincristine by the intrathecal route have been reported in Australia, the most recent in 2003.
- Two of these were fatal and one resulted in permanent quadriplegia.
- Fifty five cases have been reported internationally since 1968, the most recent in the USA in late 2005.
- There is likely to be many more cases that have not been published.

- Whilst relatively uncommon, this error results in a slowly fatal outcome in the vast majority of cases (84%) and in the few survivors, has resulted in devastating neurological damage.
- 50% of cases involve children or teenagers, 69% aged 10 years or less. Many of the cases involved patients in remission or with curable disease.

4.2. Treatment approaches

In the majority of reported cases, the error was recognised immediately, usually within minutes of the injection. One patient may have been saved via recognition of the error prior to completion of the injection resulting in only a small fraction of the dose being administered and early treatment instigated⁽¹⁹⁾. Another similar case in 1991 ended in fatality, when the error was detected prior to completion of the administration, the mis-placed fluid aspirated and the patient sent home 'as no ill effects were anticipated'⁽¹⁰⁾. In a number of cases however, the error was not identified for several hours to days^(8, 12, 14, 27) and in one recognised quite early, treatment was not commenced until four and half hours later⁽⁷⁾.

Treatment approaches reported in most cases were typically very aggressive involving attempts at removal or dilution of the vincristine and administration of agents to counteract its neurotoxic effects. Exchange of the cerebrospinal fluid (CSF), the fluid surrounding the brain and the spine, with normal saline was used in the early cases^(2, 3, 7). Following a report of a patient in whom progressive paralysis was arrested⁽⁹⁾, a more aggressive form of continuous ventriculo-lumbar CSF lavage with lactated Ringers solution and fresh frozen plasma usually in combination with intravenous and oral glutamic acid was adopted^(4, 10, 11, 13-17, 26). This approach was subsequently recommended in a number drug information sources including product information^(35,36).

Intrathecal, intravenous and/or oral corticosteroids have also been used^(3, 4, 12, 8, 11). Various other agents have been tried as antidotes including high dose intravenous folinic acid^(7,8, 11-15,17) and pyridoxine, vitamin B12 and thiamine. Hypochlorous acid is also under investigation as a possible beneficial treatment⁽³⁷⁾. The value of the individual agents is difficult to assess due to the combination with other treatments.

There have not been consistently good results following any of the treatments and implementation of preventative strategies is critical. It appears that early recognition of the error and immediate treatment with aggressive CSF washout may promote the best chances of survival once the error has occurred. The dose (as a factor of body weight) administered may also be a factor.

Salient points

- No treatment has been consistently successful in improving outcomes
- Immediate use of aggressive CSF washout appears to be the optimal approach
- An aggressive form of continuous ventriculo-lumbar CSF lavage with lactated Ringers solution and fresh frozen plasma in combination with intravenous glutamic acid may have prevented death in one patient
- The dose of vincristine and early recognition and treatment are the major factors which appear to reduce the level of neurotoxicity
- Implementation of strategies for prevention are critical

4.3. Contributing factors

Most of the case reports do not contain details of the factors found to contribute to the inadvertent administration of vincristine by the intrathecal route. As is often the case the errors occurred due to a number of interacting factors involving a combination of system and human errors. These have occurred on the background of the complexities of hospital-based care and the complexities of chemotherapy and cancer treatment and protocols. One case in the United Kingdom resulted in an external enquiry that explored the events leading to the error in detail⁽³²⁾ and details of the Australian case were also made available⁽³³⁾. Listed below are the main factors, which appeared to be involved in the case reports.

4.3.1. Concomitant prescription of an intrathecal medication

By far the most common factor in the case reports was the prescription of intrathecal doses of other cytotoxic medications to be given at the same time or on the same day as intravenous vincristine. This provided opportunity for mistakes in selection and substitution of syringes of drugs and in assumptions that vincristine syringes were to be co-administered with intrathecal therapy. The drugs most frequently implicated were methotrexate or cytarabine or triple therapy with methotrexate, cytarabine and hydrocortisone^(2-4, 7, 8, 11-18, 21, 22, 26, 27, 31,32). Many of these patients were likely to have been receiving standard national or international protocols that, to this day, require these combinations be given on the same day⁽³⁴⁾.

The fact that methotrexate solution is a yellow colour whilst vincristine is a clear solution appears not to have prevented these mix-ups^(2,8, 11, 13,14,31).

4.3.2. Storage and delivery locations of chemotherapy

Storage of intrathecal and intravenous medications in the same cupboard or refrigerator in ward areas or in the Pharmacy contributed to the selection of the incorrect drug for administration^(21, 32). This included the selection of the incorrect syringes of chemotherapy from an Oncology/Haematology ward to another location for administration^(17,27). Supply of individually packaged medications in the same outer package was reported in on case⁽³²⁾. In some cases the intrathecal and intravenous medications were to be given at the same location and hence were delivered together to the treatment room^(12, 14, 21). Differences in practices for delivery of medications across local institutions contributed to a case, where a new doctor was familiar with procedure of delivering all intrathecal medications in one coloured container, which was not the policy of his new employer⁽³²⁾.

4.3.3. Location of administration

Administration of chemotherapy at a location other than a specialist cancer ward or unit contributed to errors in several cases^(8,17, 25).

4.3.4. Labelling issues

Particularly in the early case incidents syringes of chemotherapy were prepared and not labelled^(3, 5). Instead the unlabelled syringes were placed in protective outer wraps and labels attached to these. Just prior to injection, the syringes were all removed from the protective packaging and placed on a tray. As cytarabine, hydrocortisone and vincristine are all clear solutions, mix-ups were prone to occur.

One case reported 'mislabeling of syringes' lead to the methotrexate dose being administered intravenously and the vincristine intrathecally⁽⁸⁾.

In later cases, whilst the syringes themselves were labelled, the details and in particular, the route of administration and relevant warnings, were in too small a font, were not clear or not prominently highlighted^(21, 32). In the recent Australian case, an incomplete warning label was reportedly noted⁽²⁸⁾. The fact that the volumes of vincristine injection used are often very similar to those for cytarabine and methotrexate also pre-disposes to error due to 'look a like' presentation of the syringes and packaging⁽³²⁾.

4.3.5. Staff training, experience and rostering

Inexperience of nursing, pharmacy and medical staff in the supply and administration of chemotherapy and in the related policies and procedures contributed to a number of case reports^(8,14,22,24,25, 27,31, 32,33,51). In a number of cases, junior or new staff were not closely supervised by more experienced, senior practitioners. This was for a number of reasons including rostering issues or inappropriate institutional practices whereby junior doctors were the designated staff to administer intrathecal chemotherapy^(14, 24, 25, 51). Differences in practice across institutions and lack of formal orientation and training also contributed to at least one case⁽³²⁾. In one case a doctor had been on duty for 30hours when he accidentally picked up a syringe of vincristine instead of methotrexate⁽²⁴⁾. In a number of cases, the staff member administering the chemotherapy was an experienced medical officer however not an oncologist or other specialist in cancer^(8,27) and hence may not have been aware that vincristine should only be administered intravenously.

Changeover of staff, due to interruptions and planned breaks, during the preparation of the patient or between checking and administration of medications also occurred^(21,33). A well intentioned nurse, who was possibly not familiar with the reasons behind scheduling of vincristine and intrathecal

medications on consecutive days of a protocol, disregarded the protocol to reduce the time the patient had to spend at the hospital by organising administration at the same time⁽³²⁾.

4.3.6. *Checking procedures*

Procedures adopted for unpacking and checking of medications prior to administration were an issue in a number of cases. In one example, the chemotherapy was assembled and checked off by two staff members prior to removal from outer packaging by one of the personnel. The medications were placed on a tray and administered without a second check of the syringes and labels by the administering staff member⁽¹⁷⁾. Not reading the medication labels carefully and checking them against the prescription or administration order was also reported^(17, 28,32,51).

4.3.7. *Presentation of vincristine for administration*

All cases reported in the literature involve presentation of vincristine in a syringe for intravenous administration. At least three of the cases reported, involved preparation of the vincristine dose in syringes in a 'diluted' form, one in 6.8ml⁽⁷⁾; one in 10ml⁽¹⁶⁾ and one in 20ml⁽²⁶⁾ of normal saline. One of these cases involved intraventricular administration via an Ommaya reservoir⁽¹⁶⁾. These findings are important as it is commonly thought that presentation of vincristine in syringes in volumes of 10-20ml will prevent accidental intrathecal administration.

Salient points

- Errors have occurred due to a combination of system and human error
- A number of key contributing factors can be identified:
 - Prescription of intrathecal doses of cytotoxic medications to be given at the same time or on the same day as intravenous vincristine is the most common contributing factor
 - Product presentation e.g. 'Look alike syringes' and inadequate labelling and highlighting of route of administration
 - Staff factors predominantly the level of experience and knowledge of chemotherapy and of local practices; and rostering
 - Procedural issues including delegation of authority and checking procedures
 - Errors occurred with use of vincristine diluted to 10 and 20ml in syringes

4.3.8. *Recommendations for prevention*

Given the almost invariably fatal outcome of this error, despite aggressive treatment, prevention is of the utmost importance and a number of the case reports provided recommendations for reducing the risk of recurrence. It should be noted that these are generally based on the observations of the author's and are not necessarily proven strategies. Given the dates of the early reports, some of the recommendations have already been addressed for example; some recommendations for improving dispensing and labelling of syringes have now been addressed via preparation of all cytotoxic products within Pharmacy departments rather than by the physician or at the ward level. Encouragingly, even the early reports suggested approaches aimed at reducing system error and making it harder for, well intentioned but fallible, humans to make mistakes. Only one concluded that the onus is on the physician to prevent occurrence⁽¹⁰⁾.

4.4. *Suggested strategies for prevention (from case reports)*

4.4.1. *Labelling*

- Syringes must be clearly labelled with drug name and dosage^(3, 4,8,19)
- Each syringe should be carefully labelled with the patient's name, drug, dose, route of administration, and date^(12, 16,17)
- All syringes containing vincristine must be labelled: Warning: Vincristine - for intravenous use only^(5,21,23,26)
- Include warning labels on intrathecal medications "Intrathecal Use only"^(5,17)
- Labels should have the route of administration in the largest font size and in bold⁽³²⁾

- Place the warning label on the barrel and plunger ie so it cannot be missed ⁽⁵⁾
- Label syringes and outer wraps ^(5,17)
- Use different colour or distinctive labelling and packaging of syringes and outer wraps ^(5,32)
- All syringes and over-wraps containing vinca alkaloids will have additional warning label “For intravenous use only – fatal if injected intrathecally” ⁽³¹⁾

4.4.2. Equipment

- Intrathecal syringes should have a different sized fitting from that of intravenous ones ⁽²⁶⁾
- Intrathecal syringes will be slip tip (not luer lock) ⁽¹⁷⁾
- The use of physical methods to prevent confusion is being explored including unique LP needles that can only be connected to special intrathecal syringes that are color-, size-, or shape-coded ^(17,32)

4.4.3. Presentation of vincristine for injection

- Standard mechanism to distinguish intrathecal medications from other parenteral medications ⁽²⁾
- Different sizes of syringes for intrathecal and intravenous medications ^(17,21)
- Vincristine should be given as a short infusion not as a bolus ^(17,21)
- The dose of vinca alkaloids should be diluted to at least 10ml to help distinguish it from drugs intended for intrathecal injection, for which such a large volume is rarely given ^(23,26)
- Dose of vincristine should be diluted to at least 20ml for adult patients to help reduce confusion ⁽³²⁾
- Multiple intrathecal drugs should be prepared in a single syringe ⁽²⁶⁾

4.4.4. Documentation and protocols/procedures

- All dosage calculations should be documented in the permanent charts ⁽¹²⁾
- Two qualified medical personnel (physicians and or nurse) will identify the patient, check the drug orders, read the drug labels out loud, and only the responsible physician will place the chemotherapy on the lumbar puncture tray ^(16,17,26)
- Immediately before administration of the intrathecal drug, the physician will again read out loud the drug labels to the nurse ⁽¹⁷⁾
- The orders should include the name of the specific treatment protocol and the dosages recommended ⁽¹⁷⁾
- Intrathecal chemotherapy may only be ordered by an oncology physician, and the orders must be co-signed by a similarly qualified second physician or oncology pharmacist ⁽¹⁷⁾
- Specific institutional protocols must be developed and adhered to for the administration of all chemotherapy including vincristine and intrathecal therapy ⁽¹⁷⁾
- Checking of drug names and other details on labels ⁽⁶⁹⁾

4.4.5. Separation of medications

- Intravenous and intrathecal medications should not be placed together in the treatment room ⁽²⁾
- Separate the preparation, delivery and administration of intravenous and intrathecal chemotherapy; give intravenous therapy first ^(2,12,16,21,23,26,66)
- Intrathecal drugs should be administered in a designated area for example, an operating theatre ⁽²³⁾
- Drugs for intrathecal use should be delivered to the point of use from the pharmacy at a different time and packed separately from other drugs. No other cytotoxic drugs should be delivered to or stored in such a designated area ^(17,23,26)
- Intrathecal drugs should be administered in a special treatment room, where only the intrathecal drugs and those used for analgesia/sedation are allowed ^(17, 26)
- The administering physician will be responsible for bringing the intrathecal chemotherapy to the procedure room.
- Separation in time within the protocol of intrathecal and intravenous chemotherapy would contribute to reduced risk but carries with it the burden of extended hospital or clinic stays ⁽¹⁷⁾

4.4.6. Staff training and experience

- Physicians, nurses and pharmacists involved in chemotherapy preparation, ordering, dispensing and administration should be completely familiar with the drugs' standard dosages, routes of administration, pharmacological actions and side effects ^(12,14,21,23,32)
- Medical personnel administering intrathecal medications should be required to review the case reports on intrathecal administration ⁽¹⁶⁾

- Intrathecal chemotherapy may only be ordered by an oncology physician, and the orders must be co-signed by a similarly qualified second physician or oncology pharmacist⁽¹⁷⁾
- Intrathecal chemotherapy may only be administered by an experienced physician certified in the procedure and the risks of chemotherapy. Uncertified physicians must be directly supervised. A nurse certified in chemotherapy administration must be present for intrathecal injections⁽¹⁷⁾

Salient points

Suggested preventive strategies have focused on system changes and design solutions

- Labelling – to include all patient/treatment details and highlight/warn regarding route of administration
- Separation of intravenous and intrathecal medications – in preparation, delivery, storage and timing of administration
- Staff training – only appropriately trained and experienced staff should be involved in prescribing, dispensing and administering chemotherapy
- Procedural issues – institutional policies should be developed and adhered to for all aspects of chemotherapy use including documentation and checking procedures
- Product presentation – vincristine should be prepared in 'diluted' form to reduce confusion with other syringes and the route of administration (*)
- Design solutions – different fittings and connectors for intrathecal injections and intravenous injections will prevent this error altogether

(*) Note: two fatalities have occurred despite use of vincristine diluted to 10-20ml in syringes.

4.5. Australian Data

There are three documented cases in Australia of inadvertent injection of vincristine via the intrathecal route^(27, 51,65). All were reported in the press rather than the medical literature. To determine if any further incidents have been reported, the Australian Drug Reaction Advisory Committee (ADRAC), National Coroner's Information System (NCIS) and the Australian Incident Monitoring System (AIMS) were contacted.

The Australian Patient Safety Foundation (APSF) agreed to search the National AIMS database and the South Australian database was also searched. No incidents were reported in either of these.

A search of the ADRAC database revealed one incident involving suspected intrathecal administration of vincristine reported in 2003. This case was subsequently confirmed to be one of the cases already identified⁽²⁷⁾.

The Monash University National Centre for Coronial Information (MUNCCI) conducted a data extraction from the NCIS database of coroner's findings for vincristine related death. The search used the keyword search term "vincristine" being included either in the medical cause of death or where the primary or secondary object was coded as P Drugs with a description of "other specified".

A search of the NCIS from 1st July 2000 to the present time did not identify any closed cases in which vincristine was a factor in patient deaths, where those deaths had been reported to the coroner. There was one closed case involving vincristine accidentally administered intrathecally to a patient with Burkitt's lymphoma however it appears that an inquest was not held in relation to the death.

MUNCCI also undertook a search of the TOPIC system, a local case management system that contains, inter alia, Victorian coronial findings from 1989 to 2000. The 'TOPIC' search also did not identify any cases.

The South Australian Coroner's database was also searched electronically, however, no further cases were found.

It is not possible to determine the 'true' incidence of harm related to inadvertent intrathecal injection of vincristine within our health system, or even make a best estimate. Not all deaths will be reported to the coroner and not all vincristine related incidents will be reported to AIMS or recorded in other medication incident reporting systems. Data on medication incidents relating to vincristine may be

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available in local hospital incident reporting systems. However, it is not within the scope of this project to investigate these incidents or determine the incidence of vincristine related adverse events.

It is important to note that many acute care facilities in Australia, both public and private, have already implemented risk reduction strategies for preventing administration errors with vincristine, this is discussed further below.

5. Medication alerts and recommended risk reduction strategies

5.1. United Kingdom (UK)

The greatest concentration of work on reducing the risks of inadvertent administration of vincristine via intrathecal injection has occurred in the UK. This has occurred within a wider framework of improving patient safety that is ongoing under the auspices of the National Patient Safety Agency (NPSA) and includes several key reports.

5.1.1. *An Organisation with a Memory* ⁽³⁸⁾

This report was commissioned by Health Ministers and published by the Department of Health in 2000. It reported on the findings of an expert group who, under the chairmanship of the Chief Medical Officer, reviewed the scale and nature of serious failures in the National Health Scheme (NHS), examined the extent to which the NHS had the capacity to learn from failures and recommended measures that could help to ensure that the likelihood of repeated failures would be minimised.

The group found that since 1985, 13 incidents involving inadvertent intrathecal administration of medications intended to be administered by the intravenous route have been reported in the medical literature or to the Committee on Safety of Medicines. Of these, 12 involved administration of a vinca alkaloid and ten of these were fatal. They estimated the rate of maladministration of vinca alkaloids to be 3 per 100,000 intrathecal chemotherapy treatments.

Recommendation 10 of the report, 'Identify and address specific categories of serious recurring adverse health care event' includes the recommendation that the Department of Health should establish a group to work urgently to achieve the following aim:

"By 2001, reduce to zero the number of patients dying or being paralysed by maladministered spinal injections".

5.1.2. *External Enquiry into the incident at Queen's Medical Centre* ⁽³²⁾

Unfortunately, another fatal incident involving injection of vincristine by the intrathecal route occurred in January 2001, this time at the Queen's Medical Centre in Nottingham ⁽²³⁾. This case, in an eighteen year old man, prompted an external enquiry into the incident and the events surrounding it. The findings of this enquiry also contributed to the development of national guidelines.

5.1.3. *The Prevention of Intrathecal Medication Errors. A report to the Chief Medical Officer* ⁽³⁹⁾

This review was commissioned to take forward the recommendation arising from an Organisation with a memory. It was conducted by individual consultation and adopted a systems approach to identify factors contributing to intrathecal errors and possible measures to reduce risk. The findings in relation to preventive strategies were broadly distinguished as those relating to human factors including training and education and, ward and pharmacy procedures and protocols; and those relating to equipment design (see summarised recommendations below).

Many Trusts had adopted good risk reduction strategies in relation to the human factors approach including procedures for separating the preparation, delivery and storage of intrathecal medications; separating the time, place and person administering intrathecal and intravenous medications; hazard warnings on labels and; dilution of vinca alkaloids in syringes to at least 10ml.

Limitations to the effectiveness of these were reported to be largely due to latent conditions within the system for example lack of experience and knowledge of staff, variance from procedures due to communication failures and understanding of the background to their development; the complexity and intensity of work and service pressures.

It was also noted that a lack of shared learnings across the Trusts resulted in staff having to become familiar with new protocols as they move across the system.

Vinca Alkaloids

The report referred to a number of possible additional '*pharmaceutical precautions*' and in particular with reference to the presentation of vinca alkaloids the suggestion of dispensing in 50ml or 100ml bags for intravenous infusion.

It was noted that if implemented safely this modification to practice would be equivalent to a design solution for the intrathecal hazard i.e. it would be physically impossible to connect the infusion bag to a spinal needle.

Suggested potential problems were the need to ensure drug stability at this dilution (*) and additional time taken to give the medication may increase nursing time and might result in a lower level of nursing supervision for possible extravasation.

(*) Note: this point has since been addressed ⁽⁴⁴⁾.

The author noted that, for the following decade at least, the NHS would be attempting to develop safe systems in an environment, which for historical reasons, is ill suited to the *human factors approach*. In consideration of this, risk management strategy must:

- be developed with minimal impact on stretched resources, notably staff time
- be efficient, implementing those changes with the greatest yield
- seek, where possible, to develop design solutions which will *prevent* human error in preference to human factors solutions which only *reduce the likelihood* of error
- be system-wide, with careful consideration of all consequences of change.

'The Prevention of Intrathecal Medication Errors. A report to the Chief Medical Officer' - Summary of recommendations

1. An immediate action plan be developed, implemented by a national guidance and reinforced by clinical governance at the Trust level. Key elements are:
 - Formal designation within each Trust of medical staff competent to give intrathecal chemotherapy
 - Steps to ensure that intrathecal and intravenous cytotoxic drug treatments are given at different times, by different people and in different clinical locations.
2. There should be an urgent assessment of the feasibility and safety of dispensing vinca alkaloids in an infusion bag or in a non-Luer syringe allowing intravenous administration only. This would add a level of design safety to the measures above.
3. Drug prescribing and administration errors occur with unacceptable frequency, particularly among recently qualified doctors. Steps should be taken with the Medical Schools to ensure that therapeutics and risk management are thoroughly covered in core curricula.
4. Intrathecal injection errors belong to a wider class of misconnection hazard arising from use of Luer connectors for a wide range of medical devices. Expert opinion is divided on the value of a major design initiative to achieve physical incompatibility of devices used for different routes of access. More data are required upon which to base risk-benefit and cost-benefit analyses. Key issues should be explored further with users, designers, manufacturers and international standards organisations.

5.1.4. National Guidance on the Safe Administration of Intrathecal Chemotherapy

Drawing on the learnings from these reports ^(32, 39) and after a consultation process, the Department of Health issued the '*National Guidance on the Safe Administration of Intrathecal Chemotherapy*' in November 2001 ⁽⁴⁰⁾. Following review of compliance in early 2003, an updated guidance was

released⁽⁴¹⁾. The updated guidance sets out detailed minimum requirements for NHS Trusts providing intrathecal services.

The key requirements are summarised below.

The guidance also provides an update on other relevant work including development of a competency framework for chemotherapy service delivery as well as options for equipment as a further measure to reduce risk of harm to patients through mis-connection errors.

Implementation of the guidance was supported by an audit programme, which included development of a compliance checklist and a training pack and video^(42, 43).

National Guidance on the Safe Administration of Intrathecal Chemotherapy – summary of key requirements

Leadership and risk assessment

- The Chief Executive, should identify a 'designated lead' to oversee compliance
- Risk assessments should be undertaken to ensure the safety of the service
- A written local protocol should be produced reflecting both national guidance and local information

Training and credentialing

- A register must be established and maintained which designates the personnel who have been trained and authorised to prescribe, dispense, issue, check or administer intrathecal chemotherapy
- Annual reviews of competence are required along with a formal induction programme for new staff including training appropriate to their role
- Staff moving between hospitals will take with them their certification in a training logbook, however automatic inclusion on the new hospital's register should not occur
- Intrathecal chemotherapy must only be prescribed by a Medical Consultant or associate/specialist registrar whose name is on the register
- Intrathecal chemotherapy must only be dispensed/issued by pharmacy staff on the register and must only be transported from the Pharmacy by administering doctor or pharmacy staff (on the register)
- Only Consultants and specialist/associate registrars can administer intrathecal chemotherapy.
- Under normal circumstances, intrathecal chemotherapy may only be administered during normal working hours

Documentation and checking procedures

- A purpose designed intrathecal chemotherapy chart or section within a regular chemotherapy chart must be used
- Checks should be made throughout the administration including involving the patients in the process

Separation of intravenous and intrathecal chemotherapy

- Intrathecal chemotherapy must be stored in a dedicated lockable refrigerator in the pharmacy and in the ward area (when they cannot be administered immediately)
- Intrathecal chemotherapy must be administered after intravenous chemotherapy and only following written confirmation of this
- An area should be designated for administration of intrathecal chemotherapy

National Guidance on the Safe Administration of Intrathecal Chemotherapy – summary of key requirements for vinca alkaloids:

Labelling of vinca alkaloids (vincristine, vinblastine, vindesine and vinorelbine)

For vinca alkaloids, labels should have patient name, name of product, route of administration and a clear warning of the consequences of administration by other routes – for example, **“For Intravenous Use Only – fatal if given by other routes”**.

Negative labelling (i.e. “Not foruse”) should **never** be used.

Dilution of vinca alkaloids for intravenous use

For patients over the age of 10 years, **the pharmacy should dilute the volume of intravenous vincristine to a maximum concentration of 0.1mg/ml and dispense it in a 10ml syringe as a minimum.**

For patients over the age of 10 years, the pharmacy should dilute the volume of intravenous vinblastine, vindesine or vinorelbine to a minimum volume of 20ml.

For children under the age of 10 years, intravenous vincristine, vinblastine, vindesine or vinorelbine can be given at a higher concentration (*).

(* Note: The only exception to this applies to UKCCSG (United Kingdom Children’s Cancer Study Group) Centres. These centres may choose, after a risk assessment, to give intravenous vinca alkaloids to children of any age at concentrations higher than those specified above. This practice must be covered by a waiver signed by the Chief Executive, Medical Director, Director of Nursing and Chief Pharmacist. Where a waiver is in operation, the NHS Trust must notify, in writing, the SHA Medical Director of their decision. The waiver must be reviewed annually, if renewed, resigned by all parties.

5.2. United States of America (USA)

Review of the published literature indicates that the USA has not been as prescriptive as the UK in implementation of approaches to reducing the risks of inadvertent injection of vincristine via the intrathecal route.

5.2.1. Institute for Safe Medicine Practice (ISMP)

The ISMP has published four Medication Safety Alerts that refer to inadvertent intrathecal administration of vincristine ^(18,31, 74, 77).

The first reported on problems with accidental administration of intravenous medications by the intrathecal route ⁽¹⁸⁾. The second in 2000 outlined a fatal case of intrathecal vincristine administration involving a former police chief and questioned why such tragedies continue to happen when they are so readily preventable ⁽³¹⁾. The Alerts highlight the United States Pharmacopoeia’s requirements for specific warning labels when dispensing vincristine and recommendations for safe practice (see below).

The Alerts published in 2003 ⁽⁷⁷⁾ and 2005 ⁽⁷⁴⁾ refer to further reports of fatalities associated with inadvertent intrathecal administration of vincristine. They both promote the preparation of vincristine in minibags as an additional and more fail-safe risk-reduction strategy. It is noted that this strategy:

- ensures intravenous vincristine looks very different from a syringe containing an intrathecal medication and;
- utilises a larger volume of fluid and different administration device (infusion from a bag via IV tubing), neither of which lends itself to intrathecal administration.

High-risk medication alert for vincristine injection

Institute for Safe Medicine Practice (ISMP) – Medication Safety Alert ^(18,31)

Specific cautionary labelling must be used when dispensing vincristine and labelled overwraps. This labelling must state:

“FATAL IF GIVEN INTRATHECALLY. FOR IV USE ONLY. DO NOT REMOVE COVERING UNTIL MOMENT OF INJECTION”.

Institute for Safe Medicine Practice (ISMP) – Medication Safety Alerts

‘Safe practice recommendation 1998’ ⁽¹⁸⁾

- All extemporaneously prepared syringes of vinca alkaloids should have warnings about intrathecal administration.
- Total segregation of intrathecal medications to ensure they are not prepared, delivered or administered at the same time and not administered or stored in the same location
- At least two health professionals should independently verify and document the accuracy of all intrathecal doses before administration.
- Administering personnel should review the published case reports about fatal errors with vincristine
- Medications should be provided in the most ready-to-use form to minimise the potential for error

‘Safe practice recommendation 2000’ ⁽³¹⁾

ISMP and FDA will be increasing efforts to alert healthcare industry about this problem and suggest solutions and urges readers to take the following steps to prevent intrathecal administration of IV medications:

- The list of intrathecal drugs that are administered for any disease is very small. Cytarabine, methotrexate, thiotepa, gentamicin, vancomycin, and hydrocortisone are among those used for cancer patients. Establish a list of drugs that can be administered intrathecally (or epidurally) and ban all other injectable drugs from rooms where lumbar punctures are performed.
- Require at least two health professionals to independently verify and document the accuracy of all intrathecal doses before administration. In some cases, a family member might help in the checking process.
- Wrap intrathecal drugs within a sterile bag which is then wrapped again in a sterile towel or another bag labeled for intrathecal use. Do not unwrap the package until immediately prior to injection.
- Accrediting and regulatory bodies should provide oversight to assure that facilities where chemotherapy is given have policies and procedures in place that being followed to prevent accidental intrathecal injection of IV drugs.

‘Error-reduction strategy 2003 & 2005’ ^(77, 74)

Dilute vincristine in a plastic minibag of IV fluids for slow, continuously supervised (observed) infusion to deter confusion with intrathecal syringes.

5.2.2. *Joint Commission for Accreditation of Healthcare Organizations (JCAHO)*

The most recent information was published in a Sentinel Event Alert entitled 'Preventing vincristine administration errors' by the Joint Commission on Accreditation of Healthcare Organizations (JCAHO) in July 2005⁽⁴⁵⁾. The alert refers to the fact that there is little data reported in the USA medication alert/event databases regarding administration of vincristine via the intrathecal route, noting that four cases have been reported to the Joint Commission Sentinel Event Database or the USP's MedMarx database, three of which were intercepted prior to administration and one resulting in permanent paralysis. The USP-ISMP MER has received information on eight cases, which resulted in five deaths, two injuries including quadriplegia, and one unknown outcome. It also noted that numerous cases have been reported in the US media in recent times, indicating that healthcare organisations may be not voluntarily reporting these fatal errors possibly due to concerns over legal discovery of the related information.

The Joint Commission recommendations are similar to those of the 2000 ISMP Alert⁽³¹⁾, however they also include dilution of vincristine in a minibag as the ideal.

JCAHO Recommendations for preparing dispensing and administering intravenous vincristine (and other vinca alkaloids):

1. Dilute intravenous vincristine in a volume – ideally for IV infusion in a minibag – that precludes administration via the intrathecal route.
2. If vincristine is administered via a syringe, clearly label each syringe "FATAL IF GIVEN INTRATHECALLY. FOR IV USE ONLY. DO NOT REMOVE COVERING UNTIL MOMENT OF INJECTION". Each syringe must also be placed in an over wrap carrying the same warning label.
3. Do not dispense intravenous vincristine (or any IV medication) in a manner that would permit it to be administered at a time and location where intrathecal medications are administered. If a dedicated location for intrathecal administration is not possible, the pharmacy should not dispense IV vincristine to a location where intrathecal medications are administered until it receives confirmation that intrathecal drug administration is not imminent or has been completed.
4. Conduct a "time out" with at least two qualified health care professionals to independently verify and document the drug, dose, and route at the time of pharmacy preparation of intravenous vincristine and before each administration of intravenous vincristine.

JCAHO Recommendations for drugs that are intended for intrathecal use:

1. Prepare intrathecal medications in the pharmacy as close as possible to the time of administration, label them with an appropriate short expiration time (eg eight hours), and then deliver them to and administer them in a designated (ideally separate) location, at a regular, specified time of the day or week.
2. Establish a list of drugs that can be administered intrathecally, designate specific locations where intrathecal administration may be done, and ban all other injectable drugs from those physical locations during times when intrathecal injections are being administered.
3. Conduct a "time out" with at least two qualified health care professionals to independently verify and document the drug, dose, and route at the time of pharmacy preparation of drugs for intrathecal administration and before each intrathecal administration of such drugs.
4. Wrap intrathecal drugs within a sterile bag, which then wrapped again in a sterile towel or another bag labeled: "FOR INTRATHECAL USE ONLY". Wraps or packages must be removed immediately prior to injection only by the person administering the medication.

Interestingly, the JCAHO's Proposed 2006 National Patient Safety Goals and Requirements and Rationale Statements (46) included 4 requirements aimed at reducing the risks of errors with intrathecal chemotherapy and vincristine in particular. These were not adopted and despite contacting the relevant body, there was no indication provided as to the reasons for their exclusion.

5.2.3 Food and Drug Administration (FDA)

The FDA Oncology Tools Product Label Details for Preparing Vincristine ⁽³⁵⁾ refers to the same requirements for labelling of vincristine products as the ISMP Alerts.

5.2.4 Current Practice

The MD Anderson Cancer Centre has provided vincristine doses in 25ml minibags for more than 25 years. In an Editorial, the Director of Pharmacy highlights the positive and negative aspects of this approach as compared to syringes ⁽³⁶⁾ and recommends that all Institutions utilise minibags.

'On the minus side':

- May take a little longer to prepare
- Will be bulkier
- May take a little longer to administer
- Will cost a little more

'On the plus side' – you can nearly eliminate:

- Patient deaths or serious harm from vincristine given intrathecally in error
- The resulting grief of patient's families
- Health professionals quitting their profession or experiencing emotional problems because they have harmed patients through this error
- Damage to the institution's reputation or liability issues arising from this error

Consultation with representatives of the MD Anderson regarding the success of use of minibags and issues with extravasation and paediatric patients resulted in the following comments ⁽⁶²⁾:

"...we have been working on revising our Chemotherapy Policy and have discussed the vincristine issue at length. For years on the "adult" services we had converted to administration via mini IV bag.

However, the paedics unit was still using the syringe approach. After our review of the other institutional policies from places like City of Hope, Dana Farber, NCI/NIH, ASHP, etc, and a very lengthy discussion – we recommended paedics also switch to IV minibag.

Due to the potential, irreversible and fatal outcomes if given IT, this risk far out weighed the potential vesicant risks. I think it's safe to say that in most institutions in the US it's become standard practice to give vincristine/vinblastine in IV minibag, specifically because of the safety concerns."

Policy and protocol for administration of vincristine in minibags has also been provided from the City of Hope Medical Center, Duarte, California ⁽⁷¹⁾.

The 2005 ISMP Medication Safety Alert ⁽⁷⁴⁾ reports that since use of minibags was first recommended as an error-prevention strategy in 2003:

"some healthcare providers have successfully adopted its use. Others have voiced concern, citing the risk of extravasation as a significant deterrent, especially if IV vincristine is administered via a peripheral vein. Use of a peripheral vein may be fairly common, for example, in children who have had their central lines removed after the initial phase of chemotherapy, and are now receiving monthly treatments.

Some healthcare practitioners, particularly nurses and physicians, have expressed that giving a vesicant into a peripheral vein warrants a smaller volume of solution so the nurse can continually validate venous access patency.

And yet, diluted IV vincristine can be administered at a rate of infusion similar to the undiluted form, and the patient can be monitored in the exact same manner, even if vincristine has been diluted in a small volume of fluid.

Thus, there has been some controversy regarding the safest way to administer the drug to reduce the risk of intrathecal administration without increasing the risk of harmful extravasations."

The ISMP has recently conducted a preliminary survey involving 35 US children's hospitals to determine the practices used to prepare and administer intravenous vincristine⁽⁷⁴⁾. The results showed that 23% of those surveyed were diluting vincristine in a minibag and that this approach had been adopted, ostensibly without an increase in harm from extravasation. This survey has now been expanded to include all paediatric and adult healthcare providers who administer intravenous and intrathecal chemotherapy. The survey will also seek feedback on what additional error-reduction strategies have been taken to prevent intrathecal administration of intravenous vincristine. The findings of this survey are to be reported early in 2006.

5.3 Canada

In August 2000, ISMP Canada featured that ISMP Medication Safety Alert published earlier^(31,49). A subsequent ISMP Canada Safety Bulletin reported on the publication of data supporting the dispensing of vincristine in minibags as a system safeguard⁽⁵⁰⁾. The Bulletin referred to the publication of data demonstrating the stability of vincristine diluted in minibags and syringes⁽⁴⁴⁾ and, to an editorial in the same journal, which indicated that the MD Anderson Cancer Center in the USA has been administering vincristine in 25ml of normal saline in minibags for more than twenty years⁽³⁶⁾.

The ISMP Canada noted that 'until such time as there are separate drug administration systems for IV versus intrathecal administration, the preparation of vincristine in minibags, instead of syringes, is a medication safety practice recommendation to be considered by all facilities preparing chemotherapy'.

5.4 Australia

5.4.1 The Society of Hospital Pharmacists of Australia (SHPA)

In 1995, the SHPA Committee of Specialty Practice in Oncology published recommendations for the preparation and supply of vincristine by pharmacy departments⁽⁵²⁾. The recommendations were aimed at reducing the possibility of incorrect substitution of an intravenous dose for an intrathecal dose. These recommendations were updated and their scope broadened to include recommendations for risk reduction strategies for medical⁽⁴⁷⁾ and pharmacy staff^(28,48) in 2004.

The suggested strategies are very similar to those recommended by the UK NPSA, with the addition of the recommendation to dispense vincristine diluted in minibags for both adult and paediatric patients (see below). This recommendation has also been made by other Australian oncology practitioners⁽⁵³⁾.

The authors note that while this method has been criticised as potentially increasing the risk of extravasation injury, this outcome has not been reported in the literature. Extravasation rarely occurs (< 1 in 1000 intravenous administrations) when proper techniques are followed⁽⁵⁴⁾ and the consequences are significantly less than those of intrathecal administration. It is noted that some hospitals provide vincristine in syringes diluted to 10 or 20ml as it is thought that this would prevent potential intrathecal administration. Fatalities have been reported with this approach^(16,26).

Summary of Committee of Specialty Practice in Oncology recommendations (2004)

1. Only specifically trained and designated oncology staff should prescribe, prepare, dispense and administer cytotoxic medication.
2. Medical staff must use a formal checking procedure, involving an oncology trained nurse, to ensure that the right drug is given at the right dose, by the right route, by the right method, to the right patient.
3. Intrathecal chemotherapy should only be administered in an area where no other cytotoxic drugs are available.
4. Use specifically designated containers both for transportation of intrathecal drugs from the pharmacy and for storage on the ward.
5. Intrathecal doses must be delivered separately and preferably administered after other drugs to be given by other routes are supplied to the ward and administered.
6. All intrathecal drugs must be packaged separately and clearly labelled both on the syringe and on the outer container 'For Intrathecal Use'.
7. Vincristine should be clearly labelled both on the syringe and on the outer container "For Intravenous Use Only – Fatal If Given By Other Routes". Negative labels, such as 'Not for Intrathecal Use' must never be used.
8. Consideration should be given to developing novel methods for spinal drug delivery. As a matter of design safety, standard intravenous syringes should not be able to be used for spinal administration.
9. Vincristine should be prepared in a small-volume intravenous bag rather than a syringe. For adults, vincristine can be prepared in 50ml of sodium chloride 0.9% and administered over 5 to 10 minutes. A smaller volume of fluid and slower rate of administration are suggested for children.

5.4.2 Current Practice and Extravasation

The incidence of extravasation with chemotherapy treatments has been estimated to be in the range of 0.1-6.5% of cases ⁽⁶⁶⁾ and is minimised with good administration techniques and monitoring. The incidence of extravasation associated with use of vincristine (or other vinca alkaloids) has not been formally studied. An Australian database recording extravasations and their treatment received 162 reports, none of which involved vincristine ⁽⁶⁷⁾.

To investigate current practices in dispensing vinca alkaloids and the incidence of extravasation following administration by syringe and minibag, a survey was conducted in Australian hospitals ⁽⁷²⁾.

Of 228 hospitals surveyed, 68 (29.80%) responded with 26% able to provide data, including most of the major cancer centres. In relation to vincristine, the study found that minibags were used in 43% of hospitals with dilution in 50ml sodium chloride 0.9% most common (85%). Syringes diluted to 10ml or greater were in use in 34% (20ml most common at 76%) and syringes undiluted (concentration 1mg/ml) in 20%. The major paediatric centres (6 respondents) tended to provide vincristine undiluted in syringes, however, one centre was providing vincristine in 20ml syringes.

The average length of time that vincristine had been provided in minibags was 38 months (range weeks to 150 months). From a total of over 44,300 administrations, the reported incidence of extravasation of vincristine from minibags was 0.041% (3 in 7,255) compared to the incidence with syringes of 0.03% (11 in 37,084). The data from the six paediatric centres was low however there were no cases of extravasation with minibags (0 in 42) reported. The incidence in syringes was 0.059% (8 in 13,543).

The authors noted, that there appears to be a perception, amongst some Australian oncology practitioners, particularly in the paediatric setting, that the risk of extravasation injury with syringes is less than that with infusions. Extensive literature searches and consultation with Australian practitioners have not provided information to support this. Advances in knowledge, equipment,

training and techniques have decreased the overall risk of extravasation in recent years. Further, dilution to a 50ml volume reduces the concentration of drug and hence increases the possibility of detection, and reduces the impact, should an extravasation occur. In addition, the time taken to administer a 50ml minibag would be comparable to that required for a 20ml syringe.

In conclusion, it was stated that vinca alkaloids can safely be given as a low volume, short infusion via minibag and that the adoption of policies ensuring stringent monitoring of short infusional therapy will further reduce untoward effects.

Salient points

- In Australian hospitals, it is common practice to administer vincristine to adults in a mini-bag. A volume of 50ml is commonly used.
- Paediatric centres most commonly provide vincristine undiluted in syringes, however, one paediatric centre is diluting vincristine to 20ml in syringes.
- The rate of extravasation reported with vincristine is low and was similar in minibags and syringes (0.04% versus 0.03%).
- The adoption of policies ensuring good administration techniques and stringent monitoring of short infusional therapy will further reduce untoward effects.

6. Literature on equipment and design solutions

A number of reports and expert committees have called for research into the options and viability of equipment, which would reduce or prevent the risks of inadvertent intrathecal injection of medications intended for intravenous use ^(28,39, 55, 56).

A design solution that would address mis-connection error would reduce the reliance on the various recommended human factors and potentially totally eliminate the risk of inadvertent intrathecal injection. The optimal approach would be modification of existing equipment whereby the syringes for intravenous use and spinal connectors are incompatible. This approach has also been recommended in prevention of mis-connection error with oxygen and medical gases ⁽⁷⁶⁾. Of course eliminating the potential for connection error with medications does not remove all sources of potential error. An error may still occur during the manufacturing process for example if the wrong syringe is inadvertently used or the incorrect medication is drawn up.

Approaches suggested in the literature have included improvements in syringe packaging to clearly identify intravenous therapy over-printed syringes or purpose built syringe caps incorporating shape or colour-coding ^(39,57), attachment of filters to identify intrathecal medications ⁽⁵⁸⁾, use of non-removable needles ⁽³⁹⁾ and unique connectors ^(59,60).

Unfortunately, a number of these approaches would still leave the possibility of error in the dispensing process via selection of the incorrect syringe and prototypes of new connectors/syringes have thus far been found not to be commercially viable.

A risk assessment of spinal procedures with current safeguards and proposed new connector design solutions has been published by the NPSA ⁽⁶¹⁾. The recommendations arising from this assessment included to focus further development via pilot studies and staged implementation of a non-luer compliant spinal connector for all spinal procedures i.e. not just those used for intrathecal chemotherapy.

Salient points

- A design solution, which would prevent mis-connection error, would potentially totally eliminate the risk of inadvertent intrathecal injection.
- The optimal approach would be modification to render the syringes for intravenous use and spinal connectors incompatible.
- This approach has been effective in prevention of mis-connection error with oxygen and medical gases.
- Prototypes of new connectors/syringes have thus far been found not to be commercially viable.
- Further development and review is underway.

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