

RAPID RESPONSE REPORT NPSA/2008/RRR04

Using Vinca Alkaloid Minibags (Adult/ Adolescent Units)

11 August 2008

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Background

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Following incidents of death or paralysis as a result of mal-administered intravenous vincristine by the spinal route, the elimination of harms from this cause was one of the four specific targets in the Department of Health Report 'An Organisation with a Memory'.¹ The publication of two reports relating to the prevention of intrathecal medication errors in 2001,^{2,3} led the Department of Health to issue national guidance for safe administration of intrathecal chemotherapy in 2001 and again in 2003.^{5,6}

At the same time the Department of Health established a project to oversee the development, trial and evaluation of a non-luer connector design to further reduce the risk of wrong route errors with spinal/epidural medical devices. An advertisement for a non-luer connector design to be fitted to spinal devices was placed in the OJEC European Journal in 2002.⁶ Research evaluations of the prototype connectors will be completed by summer 2008.^{7,8,9} The NPSA is planning to lead a purchasing for safety initiative and work with the healthcare industry to obtain devices with safe connectors for use in the NHS over the next three years.

WHO Recommendations

In July 2007 the WHO World Alliance For Patient Safety issued Alert 115 describing four recent patient safety incidents in different countries in which vincristine had been accidentally administered by the intrathecal route instead of intravenous route as intended.¹⁰ The Alert indicated that since 1968 this same error had been reported 55 times from a variety of institutional settings. These incidents had occurred despite repeated warnings of the risk and introduction of extensive labelling requirements and recommendations intended to standardise practice and reduce risks.

The WHO World Alliance For Patient Safety consulted expert opinion widely and recommended the following actions:

Short term:

- The labelling of vinca alkaloids should include a clear warning that reads: 'FOR INTRAVENOUS USE ONLY - FATAL IF GIVEN BY OTHER ROUTES'.
- Syringes should not be used for vinca alkaloid administration.
- Doses of vinca alkaloids should be prepared for use by dilution in small volume intravenous bags (the 'minibag' technique), rather than in syringes, to protect against accidental administration via a spinal route.

Longer term

- Research, develop and promote the separation of intravenous and spinal delivery systems so that medicines intended for intravenous administration cannot be administered by the spinal route and vice versa.

Exception

In some cases vinca alkaloids may be administered as longer running infusions using CADD pumps and elastomeric infusers. This method of administration is required in the VAD and VAMP regimens for multiple myeloma in which vincristine and doxorubicin are jointly infused over 4 days in each cycle.

Review of Evidence of Harm

Review of International Incident Reports

Although 55 incidents are reported in the WHO Alert, details of all 55 incidents are not available in the references quoted.¹¹⁻¹²

A comprehensive review of published incident reports has been undertaken by Naomi Burgess, a project pharmacist working for the Society of Hospital Pharmacists of Australia and summarises details of 32 published incidents reported up to December 2005.¹¹ Details of dose and injection volume are not available for all the reports. However, it is a reasonable assumption that the volume of vinca alkaloids administered intrathecally was less than 5ml in accordance with the manufacturers original preparations and recommendations, unless the report specifically identified that a larger volume was used.

“Larger” volume incidents

In two of the incidents reviewed by Burgess larger volume injections are specifically mentioned.

Case 1: Meggs et al from the USA reported in 1998 the case of a 59 year old woman who was administered vincristine 2mg in 10mls via an Ommaya reservoir by the intraventricular route.¹³ No explanation is given about why the volume of vincristine injection did not alert the doctor that he was about to administer the drug by the wrong route.

Case 2: Alcaraz et al from Spain in 2002 report the case of a 12 year old girl who was administered vincristine 2mg in 20ml via intrathecal route.¹⁴ Again no further information is provided to explain why the larger of volume of the vincristine injection did not alert the doctor to the potential error.

Further details on recent incidents quoted in WHO Alert 115.

Of the four recent incidents included in the WHO Alert 115, two were included in the review by Burgess and two were new cases which had occurred after completion of this review.

The Hong Kong Hospital Authority published a detailed report of the incident that occurred in July 2007.¹⁵ In the case of a 21 year old female, a prefilled syringe of vincristine 2mg in 2ml with a dispensing label including the warning ‘For IV Only’ was administered by the intrathecal route. The Hong Kong Hospital Authority has implemented a number of changes since the incident including that vincristine should be prepared in 50ml minibags when intended for administration to adults and older children. For small children dilution in a 10 – 20ml syringe is considered appropriate.

In the USA in November 2005, in a case involving a 21 year old male, a syringe containing vincristine, presumably in a volume of less than 5ml, labelled for another patient was wrongly delivered to the patient’s bedside and a doctor administered the contents of the syringe intrathecally, believing it to contain another medicine.¹⁶

The following two incidents included in the WHO report were not included in the Burgess report:

In Spain in 2005, vincristine was administered to a 58 year old female.¹⁷ The dose was prepared in a 20ml syringe, and the route of administration was not indicated on the label. The doctor asked the nurse to hand him the syringe containing the solution for intrathecal administration, and the nurse handed him the 20ml syringe containing vincristine solution. The doctor inserted the needle and began the injection. At this time, he noticed the size of the 20ml syringe and that he had

administered 2ml of vincristine solution to the patient. He discontinued administration at this point and instigated recovering procedures.

In Australia in 2004, an incident involved a 28 year old male.¹⁸ The dose of vincristine was presented in a 2ml syringe labelled "FATAL IF GIVEN INTRATHECALLY". Following the incident the hospital increased the minimum volume for vincristine syringes to 20ml and changed the alert in the label to "FOR INTRAVENOUS USE ONLY - FATAL IF GIVEN BY ANY OTHER ROUTE". Subsequently the hospital has adopted the practice of delivering vincristine in 50ml minibags.

Table 1 Summary of all published patient safety incidents identified by NPSA involving vinca alkaloids, detailed by presentation volume

Small volume vinca alkaloid syringe <5ml	Large volume vinca alkaloid syringe 10 – 20ml	Minibag of vinca alkaloid, 50ml
31 published incidents (Not all state the volume of the injection – however it is reasonable to assume <5ml)	3 published incidents 1 x 10ml 1 x 20ml via Ommaya reservoir for intraventricular administration 1 x 20ml – only 2ml administered, larger volume alerted doctor to error – and he discontinued treatment	0 published incidents

National Reporting and Learning System (NRLS)

The NPSA conducted a search for patient safety incident reports received via the National Reporting and Learning System (NRLS) involving vinca alkaloids. There were 232 such reports in the NRLS database, as at 31 March 2008¹.

Interpretation of data from the NRLS should be undertaken with caution. As with any voluntary reporting system, the data are subject to bias. A proportion of incidents that occur remain unreported, and those which are reported may be incomplete having been reported immediately and before the patient outcome is known.

Table 2: Incidents involving vinca alkaloids by degree of harm

Base: All medication incident reports involving vinca alkaloids contained in the NRLS as at 31 March 2008

Degree of harm (severity)	Number	Percent
No Harm	185	80
Low	33	14
Moderate/Severe	13	6
Death	0	-
Missing/blank	1	0
Total 232		100

¹The NRLS was first set up in October 2003 and all NHS organisations were able to report to the NRLS by 1 January 2005. It is important to note that the volume of reports received by the NRLS has steadily increased since inception, and as the NRLS is a voluntary reporting system, the data may not be representative of the rates of incidents across England and Wales.

Table 3: Incidents involving vinca alkaloids by medication error category

Base: All medication incident reports involving vinca alkaloids contained in the NRLS as at 31 March 2008

Medication Error Category	Number	Percent
Wrong / unclear dose or strength	52	22
Omitted medicine / ingredient	30	13
Wrong frequency	18	8
Wrong / transposed / omitted medicine label	16	7
Wrong drug / medicine	15	6
Wrong / omitted / passed expiry date	8	3
Wrong quantity	8	3
Adverse drug reaction (when used as intended)	7	3
Contra-indication to the use of the medicine in relation to drugs or conditions	6	3
Wrong formulation	5	2
Mismatching between patient and medicine	5	2
Wrong route	<5	**
Wrong method of preparation / supply	<5	**
Wrong storage	<5	**
Patient allergic to treatment	<5	**
Wrong / omitted verbal patient directions	<5	**
Other	40	17
Unknown	<5	**
Total 232		100

The following notation is used:

- '0' is used for percentages that are rounded down to zero;
- '-' is used for a true zero in a row/column showing per cent, i.e. when there are no cases in a category;
- '**' is used when the base number is deemed too small to provide reliable percentages (n<30).
- '***' is used when the frequency of the incident is less than 5 and the exact number and percent have been suppressed.

Details of “wrong route” incidents

“The reports of wrong route incidents found in the NRLS did not involve spinal administration. In one case the intravenous cannula had become dislodged and was sited outside the skin. In the second incident there was confusion over the prescribed route of administration for vinorelbine and in the third incident vinorelbine was prescribed and administered by the intravenous route rather than by the oral route.”

Summary from NPSA NRLS Reports

- There was no evidence of incidents (actual or potential) of the wrong route administration of vinca alkaloids by the spinal rather than the intravenous route.
- There was some evidence that vinca alkaloids are administered as longer running infusions using CADD pumps and elastomeric infusors. This method of administration is required in the VAD and VAMP regimens for multiple myeloma in which vincristine and doxorubicin are jointly infused over 4 days in each cycle.
- There were two incidents where longer running infusions of vinca alkaloids were disconnected before the four day infusion was complete.

In conclusion NPSA incident data indicated no reports of actual or potential wrong route spinal errors with vinca alkaloids and some usage of vinca alkaloids by long term infusion which had resulted in two instances of the infusion becoming disconnected before the infusion was complete, with no or low harm.

Evidence of effectiveness and practice

Evidence in favour of use of the minibag presentation of vincristine

In 2005 the Institute for Safe Medication Practices undertook a survey of vincristine presentation in the USA.¹⁹ Some 400 responses were received. It showed that about a quarter (23%) of all respondents diluted vincristine in mini-bags and half (53%) dilute the drug in syringes, before dispensing and administering it. In terms of administration for paediatrics, of the 48 responders 8% used mini-bags, 90% did not and 2% did sometimes.

In 2006 a survey was sent to 228 hospitals pharmacy departments in Australia in with a 30 % response rate (68/228) including most major cancer centres.²⁰ Records were collected over 3-120 months (average 38 months). Vincristine was provided in mini-bags by 26 of 59 (44%) institutions (most common size of 50 ml) and vinorelbine mini-bags were supplied in either 50 or 100ml. Syringes (most common being 20ml for vincristine and 50ml for vinorelbine) were used by 35 centres and 2 centres used both. Mini-bags were not used in the 5 paediatric centres that reported data.

National Policies for The use of Vincristine Minibags

Since 2005-2006 when these surveys were conducted – more National Healthcare Organisations have mandated the use of vincristine minibags and the use is expected to increase.^{11,15,16, 18, 21,22,23}

Since August 2006 in New South Wales, Australia²¹ :

- Vincristine should be administered in a minibag, not a syringe. Use of a minibag aims to ‘design out the error’ by preventing connection to a spinal needle.
- For adults – administer vincristine diluted to 50ml in a minibag over 5 – 10 minutes.
- For children – administer vincristine diluted to 20 – 50ml in a minibag over 5 – 10 minutes.
- For children younger than 10 years of age, where an individual risk assessment has determined the use of a minibag to be inappropriate, vincristine diluted in a minimum volume of 10ml may be administered from a syringe.

N.B. The administration of vincristine in shared care centres where adults and children may be treated in the same unit should be discussed locally, and wherever possible procedures should follow the practice of the feeder tertiary care centre.

In the USA the MD Anderson Cancer Centre is reported to have been preparing vincristine doses of 25ml minibags for more than 20 years.²⁴ (Note: A 25ml bag minibag is not currently available in the UK).

This Rapid Response Report should be read in conjunction with the updated national guidance on the safe administration of intrathecal chemotherapy 2008.

New or increased risks possibly associated with the use of vinca alkaloids presented in minibags

Extravasation

In the 2006 survey of 228 hospitals pharmacy departments in Australia with a 30 % response rate (68/228) including most major cancer centres²⁰, the reported incidence of extravasation from the survey was as follows:

1. vincristine extravasation from syringes 0.03% (11 out of 37,084) compared to 0.041% (3 out of 7,255) with mini-bags
2. vinblastine extravasation with syringes of 0.013% (1 out of 7,913) compared to none (0 out of 1,421) with mini-bags
3. vinorelbine extravasation with syringes of 0.029% (2 out of 6,914) compared to 0.146% (8 out of 5,475) with mini-bags – although it was noted that these cases were difficult to interpret as cases might have presented as phlebitis rather than extravasation

This gave an overall incidence of 0.027% (14 out of 51,911) extravasations with syringes compared to 0.078% (11 out of 14,151) extravasations using mini-bags. However, if the vinorelbine data is excluded, the reported extravasation rate for all other vinca alkaloids was found to be similar from syringes (0.027%) and mini-bags (0.035%) and both were infrequent. This suggests that vinca alkaloids presented in minibags did not cause an increase in the extravasation rate.

Increased vein pain associated with the infusion of vinca alkaloids

Some concerns have been reported over increased vein pain following slow infusion of vinorelbine vs bolus injection. The SPC for vinorelbine products recommend either bolus or slow infusion as the method of administration.²⁵⁻²⁷ In a randomized trial of the administration of vinorelbine by infusion and bolus injection the use of the bolus injection method did not significantly reduce the incidence of local venous toxicity compared to a six minute infusion.²⁸

The risk of mis-selection of vinca alkaloids in minibags

As part of this risk assessment, the NPSA commissioned a hospital pharmacy department to prepare a supply of simulated vincristine minibags.²⁹ The resulting products were compared in appearance to minibags containing antibiotic medicines. The labelling on the vincristine minibags indicated that the infusion was 'Chemotherapy' and 'Must Be Administered By The Intravenous Route' and "Fatal If Administered By Other Routes". However, all the labelled minibags had a uniform and, overall, poorly differentiated appearance.

Since the majority of such ready-to-administer, drug-containing infusions would be stored in pharmacy and ward refrigerators before use, there is a risk of mis-selection which could result in a dose of vincristine being administered intravenously to the wrong patient and/or instead of an intended dose of antibiotic, antiviral or other medicine.

It is recommended when vinca alkaloids are presented in a minibag then these infusions should be differentiated from other minibag infusions by the judicious use of colour and label design, following a risk assessment which takes into account the wider context of other medicines used. Further information can be found in the NPSA booklet 'Design for Patient Safety – A guide to labelling and packaging of injectable medicines'³⁰.

Drug Stability Data

A study has been conducted to evaluate the physical and chemical stability of vincristine sulphate diluted to a variety of concentrations in sodium chloride 0.9% injection and packaged in minibags to help deter inadvertent intrathecal injection of the drug.³¹

Test samples were prepared by diluting vincristine sulphate quantities of 0.5 mg, 1 mg, 2 mg, and 3 mg in sodium chloride 0.9% injection. These quantities were selected to span the range of doses normally expected in clinical use. The vincristine was diluted with sodium chloride 0.9 ml injection in volumes of 25 ml and 50 ml packaged in polyvinyl chloride minibags.

Physical and chemical stability evaluations were performed initially and after 1, 3, and 7 days of storage at 4°C followed by an evaluation at 9 days after 2 additional days of storage at a temperature of 23°C. Physical stability was assessed using visual observation in normal light and a high-intensity monodirectional light beam. In addition, turbidity and particle content were measured electronically. Chemical stability of the drug was evaluated by using a stability-indicating high performance liquid chromatographic (HPLC) analytical technique.

No physical instability was noted and no unacceptable loss of vincristine sulphate concentration was found in any sample throughout the study period. The use of vincristine sulphate doses diluted in infusion volumes of sodium chloride 0.9% injection and packaged in minibags to help deter inadvertent intrathecal administration may be performed with no unacceptable physical or chemical instability occurring.

Summary

- Previous NHS guidance in England issued in 2003 and Wales recommends that vinca alkaloids are diluted to 10ml or greater in a syringe.
- There have been reports from outside the UK of three further incidents where vinca alkaloids were accidentally administered by the intrathecal or intraventricular route despite dilution to 10ml – 20ml in a syringe.
- There have been no incidents of accidental administration of vinca alkaloids to adults by the wrong route when presented in a minibag.
- Minibags should be introduced for the treatment of adult and teenage patients being treated in adult and adolescent chemotherapy units.
- Practical difficulties of preparing and administering intravenous infusions of vinca alkaloids to treat children outweigh the benefits. For this reason the use of minibags to administer treatment to children in paediatric units is NOT recommended.
- The full range of options for treatment by broad patient type (without giving specific age ranges, given different definitions in practice of adolescent and child) and place of care are given in Table 4. Note that this advice provides consistency by place of care ie only mini-bags given in adult, adolescent or adult/adolescent units.

Table 4 Summary of recommendations for treating patients with intravenous vinca alkaloids

	PATIENT TYPE
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		Adult	Teenager	Child
CLINICAL AREA / UNIT	Adult unit	Vinca dose in a 50ml minibag	Vinca dose in a 50ml minibag	Children should not be treated in adult clinical areas. In the unlikely situation that this requirement should arise a local risk assessment should be undertaken to determine the safest method of treatment.
	Adolescent unit	n/a	Vinca dose in a 50ml minibag	Children should not be treated in adolescent clinical areas. In the unlikely situation that this requirement should arise a local risk assessment should be undertaken to determine the safest method of treatment.
	Child unit	n/a	Vinca dose in a syringe (No change to current practice)	Vinca dose in a syringe (No change to current practice)

- There is no evidence that the rate of extravasation has increased when vinca alkaloids are administered in minibags, and significant numbers of hospitals worldwide are now administering vinca alkaloids by this method.
- There is no evidence of any other significant harm being caused to patients by a change from administration of vinca alkaloids in syringes to administration in minibags.
- The National Reporting and Learning System has identified two incidents in the UK involving unintended disconnection when continuous ambulatory infusions of vinca alkaloids have been administered using electronic pumps and infusor devices. However, this practice is well established and is different from the recommendation to use minibags for short infusions when the risk of disconnection is much lower as the infusions are constantly monitored.
- To minimise the risk of mis-selection errors caused by confusion between minibags containing vinca alkaloids and those containing other injectable medicines, the judicious use of colour and careful label design to differentiate vinca alkaloids minibags is strongly recommended.
- The planned future introduction into the NHS of a new connector for the spinal/epidural route that will not connect with intravenous devices will further minimise the risks of wrong route errors with vinca alkaloids and other medicines.

Conclusion

Deaths in other countries have followed the use of vinca alkaloids diluted to 10-20ml in a syringe as is currently the practice in England. No deaths have been reported from hospitals anywhere in

which vinca alkaloids are administered from minibags. There is no evidence that the use of vinca alkaloids minibags has increased the incidence of patient safety incidents or harm of any sort. The NPSA therefore recommends that all doses of vinca alkaloids for adults and adolescents are in future administered from 50ml minibags. The risk of accidental spinal/epidural injection of drugs intended for intravenous injection will be further reduced by the eventual introduction of purpose-designed connectors for intra-spinal access which will not connect with intravenous access devices.

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