Asparaginase precipitation with ChemoClave® during sterile manufacturing

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Introduction

Asparaginase is a large modified protein (mPEG) which is used in combination with chemotherapy to treat certain types of cancers including acute lymphoblastic leukaemia (ALL).[1] It is one of the medicines which has been renamed by the Therapeutic Goods Administration (TGA) with the dual name-labelling; asparaginase (colaspase).[2] For the purposes of this poster, it will be referred to as colaspase.

Colaspase may be administered as an intramuscular (IM) injection or as an intravenous (IV) infusion which is required to be prepared in the pharmacy aseptic suite.[3] Although it is not classified as a cytotoxic, the Australian Injectable Drugs Handbook (AIDH) lists it as a non-cytotoxic antineoplastic therefore caution should be exercised during handling.[3]

ChemoClave® is a closed system transfer device (CSTD) which the Royal Melbourne Hospital (RMH) use during aseptic manufacturing when preparing cytotoxic and hazardous drugs, as pictured in Figure 1.[4] This system provides a safer alternative to using needles as it reduces the risk of operator exposure.[4]

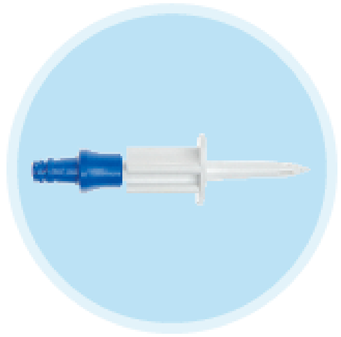

Figure 1
ChemoClave® bag spike.

Background

A 20 year-old male patient was receiving colaspase for ALL at a dose of 6,000 international units/m^2 as part of an adolescent and young adult (AYA) treatment protocol.[5] Using the Leunase® brand of colaspase as shown in Figure 2, pharmacy prepared an IV infusion of 10,000 international units in 100mL of 0.9% sodium chloride. ChemoClave® was used during preparation in accordance with the manufacturers recommendations regarding compatability.[6]

Precipitation inside the IV infusion bag was identified on the ward prior to administration. This is problematic as precipitation of an IV infusion can result in venous occlusion, thrombophlebitis as well as underdosing and consequent treatment failure. The precipitation was formed within sixty minutes after preparation and resembled small white fibrous strands. Precipitation occurred again despite remaking the colaspase using a different batch. A third bag was prepared and sourced from a precinct hospital in which precipitation was also observed. At this stage it was suspected that the ChemoClave® bag spike may have been contributing towards the precipitation.

Figure 2
Leunase® brand of colaspase

Aim

To investigate the ChemoClave® bag spike as a cause of colaspase precipitation during aseptic manufacturing.

Methods

We performed a 4-arms test whereby two bags of colaspase 10,000 international units in 100ml of 0.9% sodium chloride were prepared aseptically using a ChemoClave® bag spike and two bags of colaspase were prepared using needles.

In each group, one bag had the colaspase solution injected slowly while the other bag had the colaspase solution injected as a fast push. The same batch of drug was used to exclude batch fault.

The manufacturer of the ChemoClave® bag spike, icumedical, was notified of the precipitation issue and conducted their own independent testing under similar conditions.

Results

Precipitation of colaspase was observed in the control group where both bags were prepared with a ChemoClave® bag spike regardless of the speed of injection, although it was found that a slower injection rate produced slightly less precipitation. The bag prepared with a fast push is shown below in Figure 3. The two bags of colaspase prepared using needles did not show any signs of precipitation.

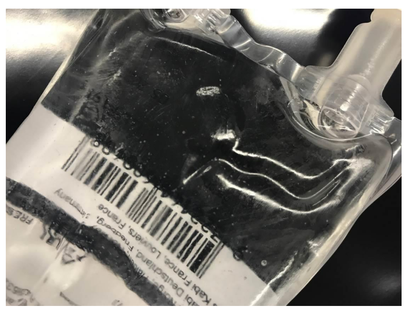

Figure 3
Precipitation of a bag of colaspase prepared as a fast push using ChemoClave®

Icumedical's independent testing yielded similar results whereby the bags of colaspase prepared using ChemoClave® precipitated shortly after preparation whilst the bags prepared using needles did not display any evidence of precipitation.

Discussion

Based on the results observed from the 4-arms test it was found that colaspase precipitated out of solution within 60 minutes of preparation if prepared using a ChemoClave ® bag spike. This is in contrast to the manufacturers recommendation listing this drug as compatible with the ChemoClave® system.[7]

Some drugs which are known to be incompatible with ChemoClave® system include abatercept and busulfan.[7] Based on these observations, it was postulated that the silicone oil-based lubricating agent used in the manufacturing of the ChemoClave® bag spike may be responsible for aggregation of large molecules and proteins such as colaspase.[7]

RMH's pharmacy department no longer uses the ChemoClave® bag spike when aseptically preparing IV infusions of colaspase. Needles are used instead as this has shown to eliminate the precipitation issues. Using needles is not without its own risks such as needle-stick injury and operator exposure hence extreme caution must be taken.

Conclusion

Colaspase is a large mPEG and may precipitate if prepared using a ChemoClave® bag spike due to a potential interaction with the silicone oil-based lubricant.

Suggestions to resolve this issue include manufacturing with needles although extreme caution needs to be taken to minimise the risk of operator exposure. Additionally, an alternative CSTD which does not use silicone oil-based lubricants may be used.

Acknowledgements

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