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Stability and Sterility Data in Pre-Filled Syringes for Zuclopenthixol Acetate and Haloperidol Used in Emergency Tranquilisation

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Abstract

Background: Needle stick injuries are a known risk in the acute hospital setting especially where the patient is agitated. The emotional burden on the staff experiencing this occupational injury is well reported, however there is insufficient data to support storing pre-filled syringes, out of the manufacturer's pack for longer than for immediate administration.

Aim: The aim was to investigate the stability and sterility of zuclopenthixol acetate and haloperidol in pre-filled syringes to allow their use as an alternative to drawing the dose from an ampoule or vial prior to administration.

Method: Two of the commonly used products in rapid tranquilisation were aseptically drawn in suitable syringes and tested for stability and sterility to establish shelf-life. Ten invited medical and nursing staff involved in rapid tranquilisation were invited to a focus group for feedback on the product practicality of use, cost and logistics of stock management.

Results: The stability and sterility tests show that zuclopenthixol acetate and haloperidol retained stability and sterility when stored under 25°C in a 3 mL disposable plastic syringes, for a period of 60 days with cost of AU$67 and AU$30 per syringe respectively.

Conclusion: The prefilled syringes provide ease and speed of administration, potential reduction in needle-stick-injuries and proved to maintain sterility. This study demonstrated that zuclopenthixol acetate 150 mg/3mL and haloperidol 15mg/3mL retained stability and remained sterile when stored under 2-8°C in plastic syringes for a period of 60 days. However the proposal was not adopted as dose flexibility was considered a greater priority than the safety gains.

Keywords: Tranquilisation; Needle-stick injuries; Stability; Sterilisation; Zuclopenthixol acetate; Haloperidol

Introduction

Needle stick injury (NSI) is a known risk in the acute hospital setting. While the prevalence is low in Australia [1] the emotional burden on health professionalsfollowingan incident is high and may require absence from duty and interruption to the person's life-style until their safety is ensured [1]. It is also known that needlestick injuries are under-reported, especially from practitioners outside the public hospital setting [2-4], with administration and re-capping needles found to be the most common causes [3].

In mental health facilities, patients who require the administration of rapid tranquilisation medications are likely to be agitated, increasing the risk of needlestick injuries for the staff administering the medication, and the supporting staff involved in the de-escalation intervention or restraining the patient. The time from the decision to administer medication to the deliverycan be critical to patient safety. The nature of this procedure does not lend itself to the use of cannulation and needle-less injection systems. The ECRI Institute [5,6] reported that 59% of health staff injuries from sharps are caused by needles.

The most common infections found with needlestick injuries in Australia were Hepatitis B, Hepatitis C and HIV [5,6]. When compared, the prevalence of positively diagnosed conditions was similar to the data from the United Kingdom and United States of America (Table 1).

The same report presented data on the direct and indirect cost of needle stick injuries. This included the investigation, treatment and lost productivity due to time off for investigations, anxiety and distress [5,6].

To gain understanding of the rapid tranquilisation (RT) process (calming without full sedation) and the dynamics of the situation, an RT administration in the hospital was attended. It was observed that the patient distress and the staff stress surrounding the whole process could easily lead to needle stick injury during the process of preparing the required dose. The nursing and medical staff feedback remains a crucial part in establishing the practicality and safety of the product.

Virus type	Australia	United Kingdom	United States of America
Hepatitis C	1.6-40%	30%	6-30%
Hepatitis B	1.8-10%	3%	1.8%
HIV	0.1-0.3%	0.3%	0.3%

*Value of Technology: Needle stick and Sharps Injuries and Safety-Engineered Medical Devices[5]&[6], at: http://www.mtaa.org.au/docs/vot/vot-needlestick-and-sharpscopytosend.pdf?sfvrsn=0. Revised on: 22/12/13

Table 1: Needlestick Injuries and transmission risks of Hepatitis C, Hepatitis B and Human Immunodeficiency Virus*.

Method

No ethical approval was required as the project involved only laboratory testing.

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Identifying the medications will be tested

The most commonly used medications in rapid tranquilisations in this facility were midazolam, haloperidol and zuclopenthixol acetate. Olanzapine was sometimes used but at the time was "special access scheme medicine," not approved or funded for general use in Australia. In addition, its form as a lyophilised powder and poor stability after reconstitution limited its potential in this context, accordingly it was not considered to be feasible. Benztropine was also used, but it was not used often and is used only after initial sedation to control side effects, when the situation has calmed. Midazolam was excluded as the Therapeutics Good Administration (TGA) of Australia had a previously established profile and identified a 60 days shelf-life, from production date, if the syringes were prepared in an approved Pharmaceutical Inspection Convention and Pharmaceutical Inspection Cooperation Scheme (PIC/S) clean room environment and aseptic manufacturing process. Accordingly haloperidol and zuclopenthixol acetate were chosen to be tested.

The products tested for stability were: zuclopenthixol acetate, clear glass single use ampule (Clopixol Accuphase™, Lundbeck Australia Pty. Ltd) 30 mg/3 mL and haloperidol glass single use ampule (Serenace™, Sigma Pharmaceuticals Pty. Ltd) 5 mg/mL, the syringes used were Becton, Dickinson and company™ manufactured 5 mL plastic disposable syringes containing a final volume of 3 mL. Storage condition of the original products was nominated to be 25°C. Acquisition of all items required and all processes and process documentation involved in aseptic compounding of these products were conducted in accordance with PIC/S. The supplier provided the testing laboratory with one batch of each of the test products. Each syringe contained the exact content of one ampule and was directly filled from that ampule. The aseptic filling process was completed in an accredited clean room utilising a laminar flow cabinet by a validated clean room technician under supervision of a registered pharmacist.

Testing after the aseptic manufacturing

Two aspects were tested, stability and sterility. Stability was tested in the TGA'sapproved laboratories and the microbiology, sterility and endotoxin content were conducted in the AMS™ Laboratories (Silverwater Australia) (AMS).

Stability testing TGA Laboratories

The method was designed (Table 2) by the TGA, based upon the methods of the British Pharmacopeia. Additional information was requested by the TGA to guide the development of the testing method; such as the desirable storage condition at the point of use in health facilities and frequency of use of the two products. The time stability trial required that:

- The pre-filled syringes must be filled by the selected manufacturer with the same commercial products as would be used in future production in accordance to the manufacturer's validated aseptic compounding process.
- The syringes used in the testing process must be the same to that will be used in future production.
- If any of the batch production conditions or material changed the stability data would no longer be valid and new stability trial would be required.

Three packs of 10 syringes of each of the two products were delivered to the TGA laboratories and the master code, batch number and expiry date for the syringes were recorded on receipt. A sample identification code was then assigned to each product by the TGA scientists and stored in a temperature controlled store room under 22 ± 1°C.

- In lots of five syringes of each medicine per time-point for plus one lot of five used as control. The pilot batch of syringes was produced and transported from the manufacturer to the TGA laboratories under the same transport conditions as to be used to deliver to the health facilities, and at the same temperature (25°C) the product will be stored during transportation of the manufacturer product requirement.
- Haloperidol syringes were tested at weeks 1, 3, 6 and 9 after receipt date, and zuclopenthixol acetate syringes were tested at weeks 2, 4, 7 and 10 after receipt date.
- The products were tested to using the methods specified in the British Pharmacopoeia 2008 (Table 2).

Sterility testing AMS laboratories

- Ten syringes of each of the two products were delivered to the AMS laboratories under the same transport conditions as to be used to deliver to the health facilities, and at the same temperature (25°C) the product will be stored during transportation of the manufacturer product requirement.
- A sample identification code was then assigned to each product by the AMS scientist and stored in a temperature controlled store room under 22 ± 1°C.
- Appearance was noted on both samples, using a 3 mL syringe of each of the two products.
- The laboratory used the Limulus Amoebocyte Lysate (LAL) kinetic chromogenic method TM125 for sample validation.

Clopixol Accuphase™ zuclopenthixol acetate 150 mg/3mL samples were initially diluted in pyrogen-free water (PFW) with 0.5%

Product / presentation	Test / procedure	Test method
Serenace™ Haloperidol 15 mg/3mL syringes for injection	Appearance	Visual inspection
	Content and ID of haloperidol	HPLC
	Related substances	TLC
	pH	British pharmacopeia
	Particulate matter (at week 9 only)	British pharmacopeia
Clopixol Accuphase™ zuclopenthixol acetate 150mg/3mL	Appearance	Visual inspection
	Content and ID of zuclopenthixol acetate	HPLC
	Related substances	HPLC
	Colour saturation at 440 nm	UV
	Particulate matter (at week 10 only)	British pharmacopeia

Table 2: Products tested to Pharmacopoeial specifications.

pyrosperse (supplied by Cambrex / Lonza) and vigorously vortexed as a pre-treatment step. Further dilution was then made in PFW to investigate the inhibition and enhancement effect by spiking a known amount of endotoxinand testing for recovery. A dilution of 1/100 in PFW was shown to have a satisfactory recovery, indicating an adequate prevention of inhibition and enhancement by the product.

Serenace™ Haloperidol 15 mg/3 mL sample did not require a pre-treatment; dilutions were made in PFW to also to investigate the inhibition and enhancement effect by spiking a known amount of endotoxin and testing for recovery. Dilution of 1/100 in PFW was shown to have a satisfactory recovery, indicating an adequate prevention of inhibition and enhancement by theproduct.

After validation tests were performed the TM125 (kinetic chromogenic) LAL test was performed on the samples.

Results

Stability tests results

The samples met the specified physical characteristics of the two products as specified in the 2008 British Pharmacopeia with no changes or trends identified in their visual appearance. There were no changes in the parent products or their related substances. The particulate matter remained within the 2008 British Pharmacopeia range. The parent product remained within the British Pharmacological requirement (2008) ranges (95-105% for Clopixol Accuphase™ and 90-110% for Serenace™) with insignificant changes recorded as 2.4% and 4.2% for Clopixol Accuphase™ and 90-110% for Serenace™ respectively. The results are shown in Tables 3 and 4. Only Haloperidol required pH testing as indicated by the British Pharmacopeia 2008.

Sterility tests results

The results for the Kinetic Chromogenic LAL assay which performed to detect endotoxin units (EU)/mL was <0.5 EU/mL (Limit is 0.5 EU/mL) for Clopixol Accuphase™ zuclopenthixol acetate and Serenace™ Haloperidol 15 mg/3mL samples (Table 5).

Clopixol Accuphase™ zuclopenthixol acetate 150 mg/3mL sample validations for sterility was conducted and growth was recovered within 72hours at respective incubation temperatures (Table 6) indicating that the sample testing procedures and specification were conducted in accordance with the test for sterility specified in the TM115 section 5, British 2008 and European Pharmacopeia 2008.

The sterility test results for Clopixol Accuphase™ zuclopenthixol acetate and Serenace™ Haloperidol 15 mg/3mL samples indicated no

Time Point	Test Results / Specifications				
	Visual appearance	Assay of zuclopenthixol acetate HPLC	Related substances (including transisomer) HPLC	Colour of the solution at 440 nm HPLC	Particulate matter BP method
	Clear yellowish oil	95-105%	Complies with BP	NMT 0.2	Complies
Week 2	Satisfactory	101.2	Complies	0.054	Complies
Week 4	Satisfactory	100.4	Complies	0.047	Complies
Week 7	Satisfactory	98.9	Complies	0.054	Complies
Week 10	Satisfactory	98.8	Complies	0.056	Complies

Table 3: Clopixol Accuphase™ zuclopenthixol acetate 150mg/3mL samples specification for stability test.

Time Point	Test Results / Specifications				
	Visual appearance	Assay of haloperidol HPLC	Related substances By TLC	pH	Particulate matter BP method
	Clear colourless solution	90-110%	Complies with BP	2.8-3.6	Complies
Week 2	Satisfactory	102.1	Complies	3.3	Complies
Week 4	Satisfactory	98.7	Complies	3.3	Complies
Week 7	Satisfactory	98.5	Complies	3.4	Complies
Week 10	Satisfactory	97.9	Complies	3.4	Complies

Table 4: Serenace™ Haloperidol 15 mg/3mL syringes for injection samples specification for stability test.

Sample Reference	LAL Assay Detection Limit Endotoxin units (EU)/mL	LAL Result EU/mL
Serenace™ Haloperidol 15 mg/3mL syringes for injection Diluted 1/100 in PFW	0.5	<0.5
Clopixol Accuphase™ zuclopenthixol acetate 150 mg/3mL Initial dilution of 1/10 in PFW with 0.5% pyrosperse made and vortexed. Further dilution then made to 1/100 in PFW	0.5	<0.5

Table 5: Kinetic Chromogenic LAL test results.

Test organism	Strain number	Media used	Incubation temperature in ºC	Inoculum A (cfu/mL)	Inoculum B (cfu/mL)	Mean (cfu/mL)	Evaluation (growth/no growth)
Staphylococcus aureus	ATCC 6538	THO	30-35ºC	35	39	37	Growth
Pseudomonas aeruginosa	ATCC 9027	THO	30-35ºC	14	17	16	Growth
Clostridium sporogenes	ATCC 11437	THO	30-35ºC	43	49	46	Growth
Bacillus subtillis	ATCC 6633	TO5	20-25ºC	70	85	78	Growth
Candida albicans	ATCC 10231	TO5	20-25ºC	19	22	21	Growth
Aspergillus niger	ATCC 16404	TO5	20-25ºC	27	34	31	Growth

Table 6: ClopixolAccuphase™ zuclopenthixol acetate 150mg/3mL and Serenace™ Haloperidol 15 mg/3mL samples validation.

Media / Incubation Clopixol Accuphase™ zuclopenthixol acetate 150mg/3mL	Observation Growth / No growth
Fluid Thioglycollate USP+ 0.5% Tween 80 at 30-35ºC / 14 days	No growth
Tryptone Soya Broth + 0.5% Tween 80 at 20-25ºC / 14 days	No growth

Table 7: ClopixolAccuphase™ zuclopenthixol acetate 150 mg/3mL sterility tests results after 60 days.

Media / Incubation Serenace™ Haloperidol 15 mg/3mL syringes for injection	Observation Growth / no growth
Fluid Thioglycollate USP+ 0.5% Tween 80 at 30-35ºC / 14 days	No growth
Tryptone Soya Broth + 0.5% Tween 80 at 20-25ºC / 14 days	No growth

Table 8: Serenace™ Haloperidol 15 mg/3mL syringes for injection sterility tests results after 60 days.

growth when treated with fluid thioglycollate USP + 0.5% tween 80 at 30-35ºC / 14 days and tryptone Soya Broth + 0.5% Tween 80 at 20-25ºC / 14 days (Table 7 and 8), which complies with British 2008 and European Pharmacopeia 2008.

Discussion

Due to financial constraints and limitation in suitable facilities and equipment for aseptic dispensing and testing, the two processes were contracted out to accredited compounding provider and laboratories. The compounder the TGA good manufacturing practice guidelines which based on the PIC/S principles, the ISO Standards 14644.1-4 and 13408-7:2012, the Australian standards AS 1386 – Cleanrooms and clean workstations for aseptic preparations.The laboratories conducting the testing were accredited by the National Association of Testing Authorities, Australia and applied the established testing methods for pharmaceutical products by those products manufacturers and the methods specified in the British Pharmacopeia 2008. This arrangement imposed some limitations on the possibility of repeating any testing to.

The sample tested (Serenace™ Haloperidol 15 mg/3mL syringes, Clopixol Accuphase™ zuclopenthixol acetate 150 mg/3mL) for stability and sterility met the Pharmacopoeial requirements (British Pharmacopeia and European pharmacopeia 2008 edition) for parameters tested, during the testing period when stored below 25°C and protected from light. No significant changes or trends were observed in the stability trial for any parameters in either product. Particulate matter was tested and was acceptable for both products.

- The tested doses (Haloperidol 15 mg/3 mL, zuclopenthixol acetate 150 mg/3mL and Midazolam 5mg/1mL) are not the only doses used. 100 mg zuclopenthixol acetate, 10-20 mg haloperidol, and benztropine 2 mg are also used.
- Prefilled syringes may be of significant use in facilities with large number of acute cases.
- There may be need to use of multiple syringes or part syringe content, which may lead to medication administration errors. Nursing staff preferred to mitigate the needle stick injury risk themselves over taking the risk of causing medication dose or administration error (measuring and drawing the dose from the original manufacturer ampule rather than discarding the excess from the pre-filled syringes).
- The short shelf life of 60 days would lead to increased turnover and wastage compared to the shelf-life of the manufacturer's ampoules and empty syringes, and was considered unlikely to be cost-effective.

Conclusion

This study demonstrated the possibility of providing a safer pre-filled syringes product when compared to current practice in many mental health facilities. Filling syringes and label them with short-drug name or description using a wound dressing-tap rather than what we achieved with this study to produce appropriately labelled pre-filled syringes which carry shelf-life, storage details, drug name/strength/dose and rout of administration, based on scientific finding rather than guessing.

This study demonstrated that Clopixol Accuphase™ (zuclopenthixol acetate) 150 mg/3 mL and haloperidol 15 mg/3 mL retained stability and remained sterile over 10 and 9 weeks respectively when stored under 25°C in disposable plastic syringes for a period of 60 days, when tested using the British Pharmacopeia and the European Pharmacopeia methods and criteria (Tables 7 and 8).

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