Stability of mixtures of ondansetron and haloperidol stored in infusors at different temperatures

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ABSTRACT

Background and objective Mixing different drugs for use in continuous infusion systems is a common practice in palliative care, but analytical study of compatibility and stability is not always available. The objective of this work is to study the stability of solutions of ondansetron and haloperidol at different concentrations and temperatures all prepared in 0.9% NaCl and stored in infusors, with all cases protected from light.

Materials and methods The high performance liquid chromatography-Ultraviolet (HPLC-UV) method was employed for the determination of the drugs. The concentrations of the admixtures were 0.15–0.25 mg/mL and 0.3–0.4 mg/mL of haloperidol and ondansetron, respectively, with a storage temperature of 25°C and 37°C.

Results All solutions were initially clear and colourless, but visible particles appear, in all cases, into the infusors after 2 days since their preparation.

Conclusion From the results obtained we can conclude that the mixtures prepared in the conditions previously described are stable less than 48 hours.

INTRODUCTION

The administration of drugs by subcutaneous infusion is routinely practised in palliative medicine. The WHO defines palliative care as ‘an approach that improves the quality of life of patients and their families facing the problem associated with life-threatening illness, through the prevention and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems, physical, psychosocial and spiritual’.¹ Their priority is to treat the physical symptoms caused by the progression of disease or the side effects of its treatment. To obtain optimal symptom control in these patients, the simultaneous administration of more than one drug is often required.² However, there are few published data on the compatibility and stability of drugs when administered together by this method.

When combinations of drugs are administered via subcutaneous infusion, drug incompatibility or loss of stability can occur. Incompatibility might cause drug precipitation or crystallisation, resulting in the blockage of the cannula, skin irritation and poor absorption.³ Physical and chemical instability may present a problem due to drug–drug, drug–diluent and drug–container interactions. Storage conditions are also important because the mixture is not usually administered as soon as it is prepared. Physical incompatibilities result in visible (precipitate, colour change, gas production) and invisible (subvisible particles, variations in pH) reactions.

Chemical incompatibilities can lead to a decrease in drug bioavailability, drug degradation and/or production of toxic products.

In the literature there are studies that have evaluated the compatibility and stability of various drug mixtures under different experimental conditions^{4–12}; however, it is necessary to extend this research to other mixtures that can be used in palliative care, the compatibility and stability of which have not yet been established.¹³

Ondansetron is an antagonist of 5-hydroxytryptamine (serotonin) subtype 3 (5-HT₃) receptors. These receptors are located at the periphery of the vagal nerve terminals and at the central level in the postrema area of the brain. Cytotoxic drugs and radiation damage the gastric mucosa, causing serotonin release from cells of the gastrointestinal tract. Stimulation of 5-HT₃ receptors causes the emission of sensory signals to the centre of the vomit. When ondansetron binds to these receptors, it blocks the emesis produced by the release of serotonin. This drug is indicated in the control of nausea and vomiting induced by cytotoxic chemotherapy and radiotherapy, and for the prevention of postoperative nausea and vomiting.¹⁴ In a previous work recently published by us, there is a revision about the stability studies of ondansetron alone and in mixture with other drugs.¹⁵

Haloperidol has been found to be very efficient in controlling agitation with or without pain, nausea and/or vomiting of central origin, intestinal obstruction, and delirium.¹⁶ Haloperidol is a conventional antipsychotic drug, and it is one of the first medicines that were used in the 20th century to treat mental illness. The stability of this drug has been studied in 5% dextrose,¹⁷ and in admixtures has been previously described with tramadol,⁸ diamorphine hydrochloride¹⁸ and scopolamine N-butyl bromide.⁵ Also, the compatibility of tertiary blends with haloperidol, tramadol and dextetropfen,¹⁹ or haloperidol, tramadol and hyoscine,²⁰ has been analysed.

The aim of this research was to investigate the compatibility and stability of haloperidol-ondansetron at two levels of concentrations and stored at two different temperatures, all of these protected from the light.

MATERIALS AND METHODS

Materials

Commercial haloperidol ampoules of 5 mg/mL (Dr Esteve Laboratory, Barcelona, Spain) and ondansetron ampoules of 2 mg/mL (Fresenius Kabi, Barcelona, Spain) were used. Sodium chloride 0.9% was obtained from Fresenius Kabi. Methanol (HPLC grade) was purchased from Merck (Darmstadt,

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Table 1 Statistical evaluation of data for different stability studies

Haloperidol 150 mg/L–ondansetron 250 mg/L, 25°C							
Haloperidol (mg/L)	Mean	SD	RSD (%)	Minimum	Maximum	Confidence level	
						Lower	Upper
3	34 426.6	2631.4	7.64	29 302	40 185	32 531	36 322.1
6	72 808	3170.59	4.35	66 262	81 551	70 912.5	74 703.5
7.5	103 573	9905.25	9.56	84 110	115 569	101 677	105 468
9	132 389	7015.76	5.30	115 031	140 775	130 493	134 285
Ondansetron (mg/L)	Mean	SD	RSD (%)	Minimum	Maximum	Confidence level	
						Lower	Upper
5	46 911.5	4837.56	10.31	40 269	56 383	42 505.3	51 317.6
10	126 782	8952.36	7.06	113 568	144 000	122 500	131 064
12.5	213 784	20 958.8	9.80	170 712	244 406	209 378	218 190
15	282 907	12 159.7	4.30	253 262	296 246	278 365	287 448
Haloperidol 150 mg/L–ondansetron 250 mg/L, 37°C							
Haloperidol (mg/L)	Mean	SD	RSD (%)	Minimum	Maximum	Confidence level	
						Lower	Upper
3	34 695.2	5055.33	14.57	27 213	50 498	32 995.2	36 395.2
6	75 862.1	4871.85	6.42	67 074	83 749	74 129.7	77 594.5
7.5	98 015.4	4211.78	4.30	87 433	104 577	96 248.7	99 782.1
9	131 384	11 391.8	8.67	112 838	152 700	129 684	133 084
Ondansetron (mg/L ¹)	Mean	SD	RSD (%)	Minimum	Maximum	Confidence level	
						Lower	Upper
5	54 124.5	4978.36	9.20	45 417.0	67 052.0	50 410.3	57 838.7
10	142 591	10 187.9	7.14	125 569	164 360	138 948	146 233
12.5	199 145	13 553.1	6.81	178 647	234 189	195 503	202 787
15	270 662	20 386.6	7.53	224 855	308 082	267 088	274 236
Haloperidol 300 mg/L–ondansetron 400 mg/L, 25° C							
Haloperidol (mg/L)	Mean	SD	RSD (%)	Minimum	Maximum	Confidence level	
						Lower	Upper
3	32 140.9	1936.97	6.02	28 945	35 592	26 927.4	37 354.3
6	67 809.2	2032.03	2.99	63 921	71 435	63 078.1	72 540.3
9	99 662.1	3550.02	3.56	90 854	104 148	94 785.4	104 539
12	154 558	7968.24	5.16	139 751	170 106	149 960	159 155
15	199 046	9161.04	4.60	184 858	218 365	194 315	203 777
Ondansetron (mg/L)	Mean	SD	RSD (%)	Minimum	Maximum	Confidence level	
						Lower	Upper
4	33 004.4	2071.03	6.27	28 479	36 324	22 967.6	43 041.2
8	85 759.5	5508.41	6.42	78 115	94 037	76 296.7	95 222.3
12	149 754	15 704.3	10.49	122 502	176 570	139 717	159 791
16	265 035	14 593.8	5.51	243 688	290 900	255 572	274 498
20	348 239	8922.38	2.56	332 641	363 157	338 502	357 976
Haloperidol 300 mg/L–ondansetron 400 mg/L, 37° C							
Haloperidol (mg/L)	Mean	SD	RSD (%)	Minimum	Maximum	Confidence level	
						Lower	Upper
3	34 390.7	5717.93	16.62	24 508	50 195	31 564.5	37 216.9
6	74 437.2	5594.48	7.52	64 662	83 112	71 611	77 263.4
9	110 952	10 204.5	9.19	96 905	138 969	108 126	113 778
12	151 654	14 133.3	9.32	132 560	177 108	148 827	154 480
15	202 465	15 095.5	7.46	163 237	222 354	199 639	205 292
Ondansetron (mg/L)	Mean	SD	RSD (%)	Minimum	Maximum	Confidence level	
						Lower	Upper
4	41 394.3	8997.07	21.73	27 092	66 656	34 902.1	47 886.4
8	106 721	14 494.8	13.58	79 022	127 928	100 228	113 213
12	175 981	17 486.2	9.94	134 287	219 521	169 488	182 473
16	254 444	35 293.2	13.87	178 709	312 767	247 952	260 937
20	353 304	34 381.3	9.73	227 277	390 679	346 812	359 796

RSD, Relative standard deviation.

Table 2 Regression equations for admixtures

Admixtures haloperidol-ondansetron (mg/mL)	Temperature	Drug	Regression equation ²³
0.150–0.250	25°C	Haloperidol	Slope: 15 717.4±871.1* Intercept: –13 829.8±5291.5* R ² =0.991
		Ondansetron	Slope: 23 688.2±2983.7* Intercept: –84 090.8±33 566.6* R ² =0.970
	37°C	Haloperidol	Slope: 15 726.0±1295.5* Intercept: –15 264.1±8744.9* R ² =0.987
		Ondansetron	Slope: 21 284.1±1766.1* Intercept: –59 512.8±19 868.1* R ² =0.986
0.300–0.400	25°C	Haloperidol	Slope: 14 018.6±803.9* Intercept: –15 524.5±7999.5* R ² =0.990
		Ondansetron	Slope: 20 243.6±1648.3* Intercept: –66 565.0±21 867.6* R ² =0.980
	37°C	Haloperidol	Slope: 13 778.8±494.0* Intercept: –9229.8±4915.2* R ² =0.996
		Ondansetron	Slope: 19 288.6±960.8* Intercept: –45 093.9±12 746.5* R ² =0.993

*SE for regression equation obtained by Statgraphics program.

Germany). Other chemicals and solvents were of analytical grade and were obtained from Merck. High-purity water (resistivity 18.2 MΩ cm) obtained by a Milli-Q water purification system (Millipore, Bedford, Massachusetts, USA) was used throughout this work.

Preparation of sample solutions

The concentrations of the mixtures were 0.25–0.15 mg/mL and 0.4–0.3 mg/mL of ondansetron and haloperidol, respectively, which were prepared in 0.9% NaCl and conserved at 25°C and 37°C for each one, and a Selecta oven (Incudigit 19 L 001246) was used for this purpose. Each one of the samples was stored in three elastomeric infusers protected from the light.

Preparation of standard solutions

For the first mixture mentioned above, four standards were prepared by adequate dilution from the sample (0.25 mg/mL ondansetron–0.15 mg/mL haloperidol) to obtain different concentrations of between 5 and 15 mg/L for ondansetron and between 3 and 9 mg/L for haloperidol admixtures, respectively. In the same manner for the second mixture, five standards of solutions were prepared by adequate dilution from the sample (0.4 mg/mL ondansetron–0.3 mg/mL haloperidol) to obtain different concentrations of between 4 and 20 mg/L for ondansetron and between 3 and 15 mg/L for haloperidol admixtures, respectively. The standards were divided into different aliquot parts, stored in Eppendorf tubes and frozen until each day of analysis.

Instrument and chromatographic conditions

HPLC analysis was performed at room temperature (~25°C) using a Shimadzu LC-6A pump equipped with Rheodyne 7125 injection valve of 20 µL and a Shimadzu SPD-6A spectrophotometric detector working at 254 nm. The signal from the detector was recorded and integrated with a chromatography data system Shimadzu C-R6A chromatopac; a LiChrospher 100 C18 (5 µm)

LiChroCART 250–4 column was employed. The mobile phase consisted of methanol:KH₂PO₄ 0.05 M, adjusted to pH 3 with H₃PO₃ (60:40, v/v) delivered at a flow rate of 1.0 mL/min. The sample injection volume was 20 µL, and triplicate injections were performed for every sample. The signal was recorded for 8 min, and the retention times were 3.6 for ondansetron and 6.6 min for haloperidol.

Physical stability study

The physical stability of both drugs was determined by visual inspection of each sample control, with no colour change or appearance of turbidity, and no precipitation and particle agglomeration. Visual inspection was done before determining the concentrations of ondansetron and haloperidol by HPLC.

Chemical stability study

Stability of the mixture was defined as retention of at least 90% of the initial mixture concentration, which was defined as 100%, and subsequent sample concentrations were expressed as a percentage of the initial concentration.

Forced degradation analysis

These studies are required to demonstrate specificity of stability indicating methods and also provide an insight into the degradation pathways and degradation products of the drug substance.^{21 22}

For this purpose five studies were made over each drug solution: acid, base, heat, UV light and hydrogen peroxide.

RESULTS AND DISCUSSION

Accelerated degradation study

The subsequent trials were carried out over each drug solution (6 mg/mL of ondansetron or 20 mg/mL of haloperidol).

pH study

Different amounts of HCl 1 M or NaOH 1 M (100, 250 and 500 µL) were added to aliquot of 500 µL of each drug. Additions

Figure 1 (A,B) Percentages of mixtures remaining at 25°C and 37°C.

of HCl and NaOH have not influenced the chromatographic signal of haloperidol. In the case of ondansetron, a new signal appears at 1.9 min when the HCl volume added was 250 or 500 μ L, being it higher when the volume and the time increase. On the other hand, the addition of NaOH about ondansetron signal gives two new signals (1.8 and 2.6 min). These signals enhanced with the volume of NaOH added and stayed constant with the time.

Heat study

Two samples of each drug were heated at 40°C and 60°C at different times (from 10 to 60 min). No significant changes were observed in the chromatograms in all cases.

UV light

One sample of each drug was subject to UV irradiation for several days. The signal of the haloperidol diminished with the time of exposition. With respect to the ondansetron a new signal appears at 2.2 min, and also increased with the time while the peak area at 3.6 min diminished with time.

Oxidants

Different amounts of H₂O₂ 3% (100, 250 and 500 μ L) were added to aliquots of 500 μ L of each drug. No effects were observed for haloperidol, while for ondansetron two new signals appeared at 1.9 and 2.8 min and whose areas enhanced with the volume of oxidant added.

Physical stability study

The mixtures stored into infusers, initially clear and colourless, precipitated after 48 hours from its preparation.

Chemical stability study

Statgraphics Centurion XVI program²³ was used for data analysis. Table 1 shows the statistical study of the data. Calibration curves were linear over the concentration range used, with acceptable correlation coefficients, as can be seen in table 2. Figure 1A,B shows the percentages remaining for each mixture at 25°C and 37°C.

CONCLUSIONS

This study evaluated the stability and the compatibility of mixtures of haloperidol and ondansetron when stored in

What this paper adds

What is already known on this subject

- The admixtures of ondansetron and haloperidol are recommended for use in palliative care.
- The stability of these admixtures is not known.

What this study adds

- This study evaluated the stability and the compatibility of mixtures of haloperidol and ondansetron when stored in elastomeric infusers at two temperatures (25°C and 37°C).

elastomeric infusors at two temperatures (25°C and 37°C). On the basis of our results, we suggest that subcutaneous infusion solutions, stored in elastomeric infusors and containing haloperidol-ondansetron (at the concentration ranges assayed), may be prepared and used with confidence for 48 hours after preparation.

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Competing interests None declared.

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