Stability and compatibility of ondansetron with haloperidol in parenteral admixtures

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ABSTRACT

Background The chemical stability of coadministered ondansetron (OND) and haloperidol (HAL) in parenteral admixtures has not been described yet.

Objective The aim of the present work is to study the chemical stability and the compatibility of OND and HAL admixtures.

Methods Normal saline solution and dextrose were used to prepare the admixture solutions of the drugs; the materials of the containers were the original plastic bags of the diluents and the stability was studied at 20°C. Compatibility was studied by visual inspection of no colour change and turbidity or precipitation appearance. The concentration of the drugs was studied by ultraviolet detection high-performance liquid chromatography. The method was validated following the Food and Drug Administration and European Medicines Agency guidelines, and the assay enables the measurement of both drugs with a linear calibration curve ($r=0.999$) over the concentration range 10–100 µg/mL, with acceptable values of linearity, precision and accuracy. Darunavir was used as internal standard.

Results Most of the admixtures have an adequate concentration until 24 hours (less than 10% of loss). 25% of the samples show a higher loss at 24 hours, and the chemical stability of these samples is 12 hours.

Conclusions The stability and compatibility of OND and HAL in the coadministered admixtures in Viaflo plastic bags with normal saline or dextrose are suggested at 12 hours.

INTRODUCTION

Drug stability studies are needed when they could be administered together at ambient temperature for parenteral dosage. Furthermore, the influence of the material where the solutions are contained has to be taken into account. The currently employed materials for clinical use such as glass, or plastics like PVC (polyvinyl chloride) and PP (polypropylene), or elastomer materials and their influence on the stability of the drugs are usually studied. Additionally, stability can be different when different concentrations of the drugs are employed. Then, the study of stability has to include the expected concentrations in clinical use.¹ Usually, the chemical stability of a drug is acceptable when the amount of the drug is from 90% to 110% of the initial value.²

Ondansetron (OND) is a drug mainly used to avoid nausea and vomiting due to cancer chemotherapy, radiation therapy or surgery. This drug is a highly selective 5-HT₃ receptor antagonist. Its mode of action to control nausea and vomiting is

not known, but it could be done by blocking the release of 5-HT in the small intestine, due to chemotherapeutic agents and radiotherapy, which initiates a vomiting reflex by activating vagal afferents via 5-HT₃ receptors. Also, postoperative nausea and vomiting may be avoided. It is interesting to know if the administration with other drugs is possible. The stability of OND in normal saline solution and dextrose was previously described,^{3,4} finding large periods of safe use (14–120 days), and its compatibility was studied with drugs such as dexamethasone sodium phosphate,⁵ morphine sulfate and hydromorphone hydrochloride,⁶ meperidine hydrochloride,⁷ or ranitidine hydrochloride.⁸

Haloperidol (HAL) is a widely employed antipsychotic drug, and it is used in the treatment of psychotic disorders, Tourette's disorder, and severe behavioural problems such as aggressiveness or hyperactivity. This drug works by decreasing the abnormal excitement in the brain, depressing the central nervous system at the subcortical level of the brain, midbrain and brainstem reticular formation. Also, HAL has antiemetic effect with no fully determined action mechanism, but the drug has been shown to directly affect the chemoreceptor trigger zone (CTZ) through the blocking of dopamine receptors in the CTZ. The stability of this drug has been studied in 5% dextrose,⁹ and in admixtures has been previously described with tramadol,¹⁰ diamorphine hydrochloride¹¹ and scopolamine N-butyl bromide.¹² Also, the compatibility of tertiary blends with HAL, tramadol and dextketoprofen,¹³ or HAL, tramadol and hyoscine,¹⁴ has been analysed.

Pharmacological agents are the principal method for palliating nausea and vomiting in patients with life-limiting diseases. If the patient does not respond to one agent, a second agent should be added, combining agents from different classes.¹⁵

OND and HAL can be used together to control vomiting and nausea in patients under cancer treatment because this admixture has been reported to alleviate intractable nausea and vomiting due to advanced cancer.¹⁶

To the best of our knowledge, the compatibility of OND with HAL has not been described yet. Just a study of the Y-site was done, obtaining a 4-hour stability, this being the maximum time period under study; this study was done by Trissel,^{17,18} testing concentrations of HAL of 2.5 mg/mL in normal saline or dextrose with 1 mg/mL of OND in both solutions, and also with 0.2 mg/mL of HAL in dextrose with 1.0 mg/mL of OND in normal saline solution. Usually, the employed perfusion solutions of OND and HAL in clinical use have

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lower concentrations. In fact, HAL may cause extrapyramidal side effects and QT prolongation at higher doses or if its use is prolonged. Also, the use of low doses of OND avoids severe constipation.

Thereby, perfusion solutions are used during larger time periods at 8, 12 or 24 hours. Then, there is a lack of the use of these drugs admixtures, which can be solved with chemical stability and compatibility studies to know how long they can be administered together without losing their efficacy.

AIM OF THE STUDY

The aim of this study is to determine the chemical stability of admixtures with OND and HAL to assure proper use in routine practice in the healthcare services.

MATERIALS AND METHODS

Materials

Active pharmaceutical ingredients OND and HAL were kindly provided by Normon Laboratories (Tres Cantos, Spain) and Kern Pharma (Terrassa, Spain), respectively. Commercial samples of OND (Lot #4080) were acquired from Normon Laboratories and HAL (Lot #405) samples were purchased from Esteve (Barcelona, Spain). Internal standard (IS) darunavir was provided by Janssen (Beerse, Belgium). High-performance liquid chromatography (HPLC)-grade acetonitrile and water were obtained from Teknokroma (Barcelona, Spain) and HPLC-grade methanol was obtained from Merck (Darmstadt, Germany). Potassium dihydrogen phosphate was obtained from Panreac (Barcelona, Spain). Normal saline solution (0.9% sodium chloride) (Lot #16G08E7T) and 5% dextrose in 0.9% sodium chloride (Lot #16G07E7A) were purchased from Baxter (Ribarroja del Turia, Spain).

Methods

The employed equipment was a Shimadzu LC-20AD pump with a DGU-20AS degasser and SIL-20AC autosampler, an oven CTO-10AS, and a UV detector SPD-M20A with a deuterium lamp, and the selected wavelength was 254 nm. The temperature of the oven was 35°C. The employed conditions to analyse OND/HAL admixtures were obtained using a Mediterranean SEA18 C-18 column (5 µm, 15×0.4 mm). Mobile phase was a mixture of 0.037 M potassium dihydrogen phosphate buffer solution (pH 4.3±0.1), acetonitrile and methanol (40:50:10, v/v) at a flow rate of 1.0 mL/min. Darunavir was used as IS at a final concentration of 25 µg/mL.

Preparation of stock solutions, calibration standard and quality control samples

Starting from the raw materials, stock solutions were prepared in methanol: one with 1.0 mg/mL of OND, another with 1.0 mg/mL of HAL and the last one with 5.0 mg/mL of darunavir (IS). Stock solutions were stored and protected from light at 4°C. Then, solutions with 100 and 10 µg/mL of each drug and 250 µg/mL of IS were prepared by adding methanol and mixing using a vortex for 30 s. Finally, they were used to prepare the calibration standards (n=5) and quality control samples (n=3). The used amount of the solutions of OND and HAL was in function of the desired concentration of the calibrator. Using a micropipette, 50 µL of the 250 µg/mL darunavir solution was added. The final concentration of the IS was 25 µg/mL. The total volume was achieved by adding mobile phase until 500 µL. Five concentrations were used to prepare the calibration standards for OND and HAL: 10, 40, 60, 70 and 100 µg/

Table 1 Prepared ondansetron and haloperidol admixtures in 250 mL solutions

Sample	Sample preparation		Solution
	Ondansetron (mg)	Haloperidol (mg)	
1	8	5	Saline
2	8	10	Saline
3	8	15	Saline
4	8	20	Saline
5	16	5	Saline
6	16	10	Saline
7	16	15	Saline
8	16	20	Saline
9	8	5	Dextrose
10	8	20	Dextrose
11	16	5	Dextrose
12	16	20	Dextrose

mL. Three quality control samples were used at concentrations of 20, 50 and 80 µg/mL.

Sample processing

Perfusion solutions were prepared following the usual procedure in clinical use. Commercially used OND has a concentration of 8 mg/4 mL. Then, one or two phials were used to prepare each sample. In the case of HAL, the amount was 5 mg in 1 mL. Thus, one to four phials were used to prepare the admixtures. The content of the commercial ampoules of OND and HAL were added to 250 mL of normal saline solution or dextrose in *Viaflo* polyolefin plastic bags. The prepared admixtures were not protected from light and stored at room temperature. Then, the samples were homogenised by manual agitation for 30 s, and the concentration of the different drugs was measured by HPLC at 0, 8, 12 and 24 hours. The prepared admixtures to be studied are summarised in [table 1](#).

Compatibility determination

The compatibility 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 of the determination OND and HAL concentrations by HPLC.

Validation of the analytical method

Validation of the method was carried out according to the described procedures in the guidelines for Bioanalytical Method Validation published by the Food and Drug Administration (FDA)¹⁹ and the European Medicines Agency (EMA)²⁰ with respect to specificity, selectivity, linearity, precision, accuracy, and stock and working solutions stability. Also, forced degradation studies were done under acidic, basic and oxidative conditions to analyse the possible presence of interference peaks. For more information, see online supplementary file.

Applicability of analytical method

This assay was used to quantify the OND and HAL concentrations in perfusion solution. To realise this, 450 µL of each sample was added to 50 µL of the working solution of the IS at different times (0, 8, 12 and 24 hours), and they were homogenised. Then, the analysis of each sample was done twice by HPLC and an average was obtained.

Table 2 Mean percentage values of OND and HAL concentrations at different times remaining in the admixtures

Sample	pH	Time (hours)							
		0		8		12		24	
		OND (µg/mL)	HAL (µg/mL)	OND (%)	HAL (%)	OND (%)	HAL (%)	OND (%)	HAL (%)
1	3.98	40.65	13.49	104.72	105.88	107.84	109.67	95.57	95.64
2	3.81	39.68	37.52	108.29	109.26	106.40	108.54	99.48	97.82
3	3.69	42.79	67.91	98.79	99.10	104.54	105.44	92.15	93.13
4	3.62	41.64	94.79	100.59	100.37	104.11	104.14	91.44	90.11
5	3.87	83.42	16.08	99.68	98.57	105.07	105.77	88.65	80.73
6	3.78	82.30	39.07	101.35	103.04	103.66	105.65	89.51	87.77
7	3.67	79.70	64.40	109.02	109.51	109.20	108.03	92.37	91.78
8	3.62	77.20	88.17	109.94	107.60	108.52	109.81	95.52	93.90
9	3.95	40.52	16.53	100.61	99.48	108.52	109.06	96.10	92.10
10	3.65	41.35	87.27	98.52	97.99	109.39	107.43	91.52	90.87
11	3.93	79.94	14.05	99.19	97.59	106.59	106.17	93.20	86.96
12	3.66	82.24	89.85	96.06	95.32	98.86	98.67	87.84	86.07

HAL, haloperidol; OND, ondansetron.

RESULTS

The validation of the analytical technique was done with good results in terms of specificity, selectivity, linearity, precision and accuracy. Also, the stock and working solutions have shown good stability values. Finally, under the forced degradation conditions, no interference peaks were shown (see online supplementary file).

All the studied samples do not present any colour change, appearance of turbidity or precipitation.

Sample preparation and the obtained values of drug concentrations at 0, 8, 12 and 24 hours are presented in table 2. All the admixtures are inside the appropriate range concentrations (90%–110%) until 12 hours. After 24 hours, four blends (5, 6, 11 and 12) have shown loss in drug concentrations with less than 90% of the initial value; for these cases, the maximum for chemical stability is 12 hours. The rest of the samples have an acceptable concentration of the drugs even at 24 hours.

DISCUSSION

The combination of drugs in a single solution in palliative care permits the administration of smaller volumes, reduces the number of pumps and prevents stress on the veins. Nausea and vomiting are controlled by administering combinations of antiemetic agents, such as HAL and OND. HAL is preferred over other antiemetics because it causes less sedation or skin irritation, so mixtures containing HAL and other drugs have been reported for parenteral infusion in terminally ill patients with cancer.²¹

The quantification of HAL and OND was validated with this assay by the FDA¹⁹ and EMA²⁰ requirements, and it can be implemented to measure these drugs' concentration in the routine analysis of the perfusion solutions of patients under treatment with OND and HAL. The studied parameters during the validation of the analytical method were found satisfactory in terms of specificity and selectivity, range of study, linearity, precision, accuracy, and stability of the working solutions, and this method can be implemented to carry with stability and degradation studies of OND and HAL admixtures.

Compatibility was shown by the no colour change and precipitation or turbidity appearance. Also, the observed pH values are between 3.62 and 3.98, which are acceptable values for

perfusion solution.²² For large duration treatments with these admixtures, there is a risk of phlebitis.

The application of the method to study the chemical stability of the admixtures of OND and HAL for patients to avoid their nausea and vomiting has been tested. Showing the concentration values in function of the time, the stability of the OND/HAL admixtures can be defined at 12 hours for all the studied samples with concentrations from 0.032 to 0.064 mg/mL of OND and from 0.02 to 0.08 mg/mL of HAL, solved in normal saline solution and in 5% dextrose.

All the studied samples present a decrease in their drug concentration at 24 hours, with four of them being out of the desired range of concentrations to accept their chemical stability (admixtures 5, 6, 11 and 12). But a 12-hour chemical stability in clinical use is suggested to assure the desired OND and HAL concentrations.

CONCLUSIONS

The compatibility of the OND/HAL admixtures for perfusion administration was studied, finding 12-hour stability for all the studied samples. Most of the studied samples also present 24-hour stability. Higher chemical stabilities are desirable for the perfusion of the drug admixtures. But in the case of the coadministered OND and HAL, the recommended value of chemical stability is 12 hours. Further studies using infusors (elastomeric material) are needed to analyse the chemical stability of the OND and HAL admixtures for longer administrations periods. A validated method following the agencies' requirements was followed, with good results of precision, accuracy and stability of the working solutions.

What this paper adds

What is already known on this subject

- The admixtures of ondansetron and haloperidol are recommended to be used in the clinical setting, but their stability is not described.

What this study adds

- The stability of ondansetron and haloperidol admixtures is demonstrated until 12 hours in all the studied cases.

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