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Chemical stability of ondansetron hydrochloride with other drugs in admixtures via parenteral; a review

Revisión de la estabilidad química del ondansetrón con otros medicamentos en mezclas de administración parenteral

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Abstract

Objective: This review was prepared to offer the most complete information about the use of ondansetron in parenteral admixtures with other drugs.

Method: The search was done from September 2016 to April 2017 by using electronic databases Stablis[®] and Micromedex[®] solutions, Medline/PubMed and Scholar Google searching publications about ondansetron stability in parenteral infusion when is administered by itself or with other medication.

Results: 49 studies are included with a total of 53 drugs. 15 drugs were found compatible administered with ondansetron in a clinical routine concentration range in intravenous administration. Also, four ternary blends were found compatible and another one was incompatible. Otherwise, 38 drugs were found incompatible.

Conclusions: Compatibility of ondansetron offers a broad number of options to be used to avoid nausea and vomiting symptoms in patients with other concomitant medication.

KEYWORDS: Ondansetron++ Chemical stability++ Oncology++ Nausea++ Palliative medicine.

Resumen

Objetivo: Esta revisión ha sido preparada para recopilar toda la información referente a la estabilidad del ondansetrón en mezclas parenterales junto a otros fármacos.

Método: La búsqueda fue realizada entre septiembre de 2016 y abril de 2017 empleando bases de datos electrónicas como Stablis[®] y Micromedex[®] solutions, Medline/PubMed y Google Académico buscando publicaciones sobre la estabilidad del ondansetrón para infusión vía parenteral cuando es administrado en monoterapia o en una mezcla con otros fármacos.

Resultados: En este trabajo han sido incluidos 49 artículos con un total de 53 fármacos. 15 fármacos han sido descritos como compatibles con ondansetrón en concentraciones habituales en la clínica práctica para administración intravenosa. Además, cuatro mezclas ternarias han sido descritas como compatibles y una como incompatible. Por

otro lado, 38 fármacos han sido descritos como incompatibles para su administración con ondansetrón.

Conclusiones: La compatibilidad del ondansetrón ofrece un amplio rango de opciones para evitar los síntomas de náuseas y vómitos en pacientes con otra medicación concomitante.

PALABRAS CLAVE: Ondansetrón, Estabilidad, Oncología, Náusea, Medicina paliativa.

Introduction

The use of intravenous drugs under combination has advantages against the individual use of each one. But, to mix them is important to know the stability of the admixture. This parameter is usually defined as a remaining 90% of the initial value of each drug. Another important parameter is the compatibility of the admixture and it makes reference to the physicochemical parameters as colour change, presence of turbidity and precipitate or changes in the pH values or osmolality. Changes in the concentration of the drugs and in their compatibility can be due by degradation, chemical reactions or physical incompatibilities. If the value of the concentration decrease under 90% or if a compatibility change is observed, the admixture is not stable and it can not be administered to the patients.

Also, microbiological stability should be taken into account. This parameter depends on the place of preparation, time and the presence of different microorganisms. Microbiological stability usually is assigned by using a microbiological risk matrix¹ and it depends of the type of drugs, its preparation procedure or the temperature of storage.

Ondansetron is an antiemetic drug mainly used to avoid nausea and vomiting produced by cancer chemotherapy, radiation therapy, surgery and other. This drug is a highly selective 5HT₃ receptor-antagonist. The ondansetron mode of action to control of vomiting and nausea is not described yet. One possibility could be done by blocking the release of 5HT in the small intestine, due by the chemotherapeutic agents and radiotherapy, which initiates a vomiting reflex by activating vagal afferents via 5HT₃ receptors. Also, ondansetron can avoid the post-operative nausea and vomiting. Thus, patients who required ondansetron to avoid vomiting and nausea usually have another medication as chemotherapeutics, corticoids or sedative drugs having most of them reported incompatibilities. To administer the correct treatment to the patients is needed to choose a compatible mixture. Ondansetron is mainly administered via parenteral in the clinical routine practice. The availability of venous access is limited and if various drugs are administered to the patients is necessary to study the co-administration of the drugs mixing them in the same solution. Also, mixing drugs a reduction in the liquid volume is acquired. This reduction is highly recommended in renal insufficiency, heart disease or elderly patients and in the subcutaneous administration by infusion bags or infusers. Then, it is interesting to know if the administration of ondansetron with other drugs is possible.

Methods

Search strategy

We have performed a search for articles published in English language through Medline/PubMed and Scholar Google. The following keywords were used: (“ondansetron”) and (“stability” or “compatibility” or “coadministered” or “admixtures”). In PubMed the search details were: “ondansetron(Title) AND (stability(All Fields) OR compatibility(All Fields) OR admixtures(All Fields) OR coadministered(All Fields))” founding 61 articles. A similar searching in Scholar Google provides 57 articles. Finally, the data presented in the electronic databases Stabilis[®] and Micromedex[®] solutions and in the was taken into account to complete the review adding 19 more articles to the search. The PRISMA² recommendations have been followed to prepare this review about the ondansetron stability.

Sampling methods

Studied articles in this review use intravenous admixtures. Plastic syringes and Y-site administration were discarded, except in case of Y-site incompatibilities. They were taken into account because these combinations will be also incompatible for infusion bags administration.

The terms room or ambient temperature are used in this review and they make reference to 20-25 °C. The accepted levels of stability are a remaining percentage of the drugs higher of 90%.

Results

The present review describes first the stability of ondansetron hydrochloride at different temperatures. After that, the stability of ondansetron when is co-administered with other drugs in intravenous administration is exposed and finally, the published incompatibilities of ondansetron with other drugs are presented. The summary of the search and work done is presented in a flow diagram in Figure 1.

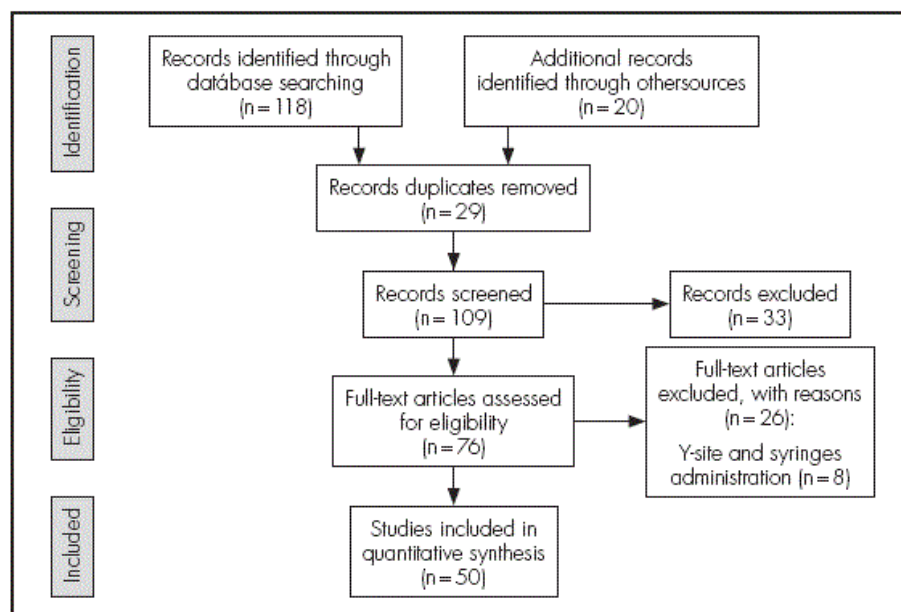


Figure 1

Flow diagram of the search and preparation of this review.

Excluded records were in base of a repetition of the article or because obtained information was based in subcutaneous or Y-site administration, being the required compatibility of the admixture larger in case of parenteral administration.

The stability of ondansetron with other drugs was studied with 53 drugs coming from a total number of publications of 49. In case of ondansetron compatible admixtures fifteen drugs were described. Otherwise, 38 drugs were found incompatible. Also, five ternary blends were studied being four compatible and another incompatible.

Ondansetron chemical stability

Previously to describe the ondansetron chemical stability with other compounds, a description of its own stability is necessary. When the drug is stored at -20 °C in normal saline or dextrose in a concentration range from 0.25 to 1 mg/ml the reported chemical stability is at least 90 days³⁻⁵. At 4 °C, most of the published articles found a 14 days stability for ondansetron solutions with concentrations from 0.024 to 1 mg/ml in normal saline and dextrose 5%^{3,4,6,7}. Also Ringer injection⁸ was found compatible with ondansetron hydrochloride (0.016 mg/ml) for seven days at refrigerated temperature. When ondansetron (0.24 mg/ml) is refrigerated in an elastomeric device for pump infusion, its demonstrated chemical stability is 31 days⁹. Furthermore, in case of ambient temperature (22-25°C), 48 hours of chemical stability are reported by most of the authors in the concentration range between 0.03 and 1 mg/ml in normal saline solution and dextrose^{3,4} and chemical stability of ondansetron (0.024-0.096 mg/ml) in lactate Ringer injection⁶ was fourteen days at room or refrigerated temperature.

Finally, when ondansetron is delivered by a portable infusion-pump reservoirs at near-body-body temperature (30 °C) a chemical stability up to 24 hours for 0.24 mg/ml and up to one week was reported for 2 mg/ml samples⁹.

Ondansetron chemical stability coadministered with other drugs

Admixtures with ondansetron and other medication were evaluated to determine their compatibility.

Therefore, for additional pain treatment, ondansetron can be blended at different conditions/concentrations in binary mixtures with meperidine hydrochloride¹⁰, tramadol¹¹, hydromorphone hydrochloride and with morphine sulfate¹². Otherwise, ondansetron hydrochloride and naloxone hydrochloride admixture was also studied¹³.

Ondansetron plus another immunosuppressant or antiemetic treatment mixed in the same solutions was also demonstrated (dexamethasone sodium phosphate^{14,15}, methylprednisolone¹⁶, fosaprepitant¹⁷).

Additionally it is compatible with chemotherapeutic agents like cyclophosphamide with dextrose and normal saline solution¹⁸, cisplatin¹⁹, cytarabine, doxorubicin hydrochloride, etoposide and methotrexate sodium²⁰.

Also for binary mixtures, recently a twelve hours chemical stability has been found for ondansetron/haloperidol admixtures at room temperature in normal saline solution or dextrose²¹.

A summary with the stability results of the admixtures that can be used in clinical practice is presented in Table 1.

Table 1
Described stabilities of ondansetron with other drugs

Drug	Concentration (mg/ml)	Ondansetron concentration (mg/ml)	Diluent	Material	Conservation	Temperature (°C)	Time
Cisplatin	0.45	1.09	NSS	PVC ^a	PL	30	7 days
Cisplatin	0.20	0.48	NSS	EL ^d	PL	30	24 hours
Cyclophosphamide	0.3-2.0	0.05-0.4	NSS & D5W	PVC	L	23-25	4 days
Cyclophosphamide	0.3-2.0	0.05-0.4	NSS & D5W	PVC	L	4	8 days
Cytarabine	0.2-40.0	0.03-0.3	D5W	PVC	L	21-23	48 hours
Dexamethasone sodium phosphate	0.2-0.4	0.15	NSS & D5W	PVC	PL	4 & 25	28 days
Doxorubicin hydrochloride	0.1-2.0	0.03-0.3	D5W	PVC	L	21-23	48 hours
Etoposide	0.1-0.4	0.03-0.3	D5W	PVC	L	21-23	48 hours
Fosaprepitant	1.0	0.07	NSS	Not cited	L	25	24 hours
Haloperidol	0.02-0.08	0.032-0.064	NSS & D5W	PO ^b	L	21-23	12 hours
Hydromorphone hydrochloride	0.5	0.1-1.0	NSS	PVC	PL	4 & 22	31 days
Meperidine hydrochloride	4.0	0.1-1.0	NSS	PVC	Not cited	4 & 22	31 days
Methotrexate sodium	0.5-6.0	0.03-0.3	D5W	PVC	L	21-23	48 hours
Methylprednisolone	2.40	0.16	NSS	PO	L	20-25	24 hours
Methylprednisolone	2.40	0.16	NSS	PO	Not cited	4	48 hours
Morphine sulfate	1.0	0.1-1.0	NSS	PVC	PL	4 & 22	31 days
Naloxone hydrochloride	0.2	0.4	NSS	PP ^c	L	4 & 22	8 days
Tramadol	10.0	0.08	NSS	PO	L	4 & 22	14 days

NSS: Normal saline solution; D5W: 5% dextrose; a = PVC: polyvinyl chloride; b = PO: Polyolefin;
c = PP: Polypropylene; d = EL: Elastomer. L = light exposure; PL = protection from light

Finally, ternary blends have been studied. Ondansetron (0.44 mg/ml), dexamethasone sodium phosphate (0.28 mg/ml) and lorazepam (0.028 mg/ml) in dextrose 5% solution at ambient light and temperature have demonstrate a 24 hours of chemical stability²². Admixtures with ondansetron, doxorubicin and other chemotherapeutic agent were also tested at 30 °C²³, but it is not cited the light storage conditions; ondansetron (0.48 mg/ml), doxorubicin (0.4 mg/ml) and vincristine sulphate (0.014 mg/ml) in normal saline and elastomer have shown 24 hours of chemical stability. Change the material to PVC and increasing the concentrations of each drug to the double, the shown chemical stability increases until five days. With dacarbazine (8 mg/ml), ondansetron (0.64 mg/ml) and doxorubicin (0.8 mg/ml) at 30 °C in elastomer or PVC have shown 24 hours stability. Recently a physicochemical stability of 15 days for mixtures containing fosaprepitant (0.6-3.0 mg/ml), ondansetron (0.03-0.16 mg/ml) and dexamethasone (0.03-0.16 mg/ml)²⁴ in viaflo infusion bags have been established under different storage conditions of light (4 and 25 °C) and temperature (under light exposure or protected from light).

Ondansetron incompatibilities

Several incompatibilities of ondansetron with other drugs have been reported (physicochemical incompatibility, precipitation due to pH of the solution)²⁵⁻⁵¹. For example, dantrolene sodium precipitates from solutions with a pH less than 8.8, including dextrose and sodium chloride solutions. Then the combination with ondansetron is not possible in these solutions⁴³.

Another like azathioprine sodium or cefepime hydrochloride and ondansetron (1 mg/ml) in normal saline or dextrose were found incompatible by Y-site administration simulation at room temperature^{37,38}.

Also, biologic compounds as trastuzumab⁴⁹, rituximab⁵⁰ and gemtuzumab ozogamicin⁵¹ were found incompatible with ondansetron in normal saline solution.

As a general view, Table 2 summarizes the incompatibilities.

Table 2
Incompatibilities of ondansetron with other drugs

Drug	Concentration (mg/ml)	Ondansetron concentration (mg/ml)	Diluent
Acyclovir sodium	7.0	1.0	NSS
Allopurinol sodium	3.0	1.0	NSS
Aminophylline	2.5	1.0	NSS
Amphotericin b	0.6	1.0	D5W
Ampicilin sodium	20.0	1.0	NSS
Amsacrine	1.0	1.0	D5W
Azathioprine sodium	13.33	1.0	NSS & D5W
Cefamandole nafate	333.0	1.0	NSS & D5W
Cefepime hydrochloride	20.0	1.0	D5W
Cefoperazone sodium	40.0	1.0	NSS
Ceftobiprole	2.0	1.0	NSS & D5W
Chloramphenicol sodium succinate	333.0	1.0	NSS & D5W
Dantrolene sodium	0.8	1.0	NSS
Ertapenem solution	20.0	1.0	NSS
Fluorouracil	16.0	1.0	NSS
Foscarnet sodium	24.0	1.0	NSS & D5W
Furosemide	3.0	1.0	NSS
Ganciclovir sodium	20.0	1.0	NSS
Gemtuzumab ozogamicin	0.1	1.0	NSS
Inamrinone lactate	2.5	1.0	NSS & D5W
Indomethacin sodium	1.0	1.0	NSS & D5W
Lansoprazole	0.55	1.0	NSS & D5W
Lorazepam	0.1	1.0	NSS
Lornoxicam	0.4	0.08	NSS
Meropenem	50.0	1.0	NSS
Methohexital sodium	2.0	1.0	D5W
Micafungin	1.5	1.0	NSS
Pantoprazole sodium	0.4	1.0	D5W
Pemetrexed disodium	20.0	1.0	NSS & D5W
Pentobarbital sodium	25.0	1.0	NSS & D5W
Phenobarbital sodium	65.0	1.0	NSS & D5W
Phenytoin sodium	25.0	1.0	NSS & D5W
Piperacilin sodium	40.0	1.0	NSS
Rituximab	4.0	1.0	NSS
Sargramostim	10.0	0.5	NSS
Thiopental sodium	25.0	1.0	D5W
Trastuzumab	1.5	1.0	NSS

NSS = Normal saline solution; D5W: 5% dextrose.

Finally, the ternary blend with ondansetron (0.008 mg/ml), mesna (1.25 mg/ml) and furosemide (0.02 mg/ml) was found chemically unstable³⁶.

Discussion

The described combinations of ondansetron with other drugs offers a wide range of therapeutic options and also, avoids the fallacious use of many combinations. But, there is a lack in the published chemical stability works of ondansetron with other concomitant medication in admixtures and there are unpublished possible clinical routine combinations in infusion bags for palliative medicine.

Then, new research studies can be developed to cover the lacks. The study of the chemical stability of ondansetron with other drugs in

infusion bags for parenteral administration used in cancer treatment, palliative medicine or others can improve the treatment of many patients.

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Notes

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Conflict of interest declaration

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