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Research Article

SYSTEMATIC REVIEW OF COMPATIBILITY OF INTRAVENOUS ACETAMINOPHEN AND KETOPROFEN ADMIXTURE

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ABSTRACT

Intravenous administration of acetaminophen and ketoprofen admixture is a common practice among health care providers in hospitals without consideration to their compatibility and stability. Therefore, the aim of this systematic review is to assess the stability and physical and chemical compatibility of intravenous acetaminophen and ketoprofen admixture and to evaluate the quality of the data in these studies. An extensive electronic literature search was conducted on MEDLINE, HINARI, Google scholar database as well as international pharmaceutical peer-reviewed journals to identify original research articles published in the English language from inception to April 2019 on the topic. The quality of the included data was assessed with defined parameters for physical and chemical compatibility. Only five articles fulfilled all inclusion criteria, therefore they were selected and analyzed. Studies imply that acetaminophen and ketoprofen mixtures were stable and compatible physically and chemically, showing neither loss of concentration nor degradation products over 24 to 48 hours.

Keywords: acetaminophen, ketoprofen, compatibility, stability, admixture.

INTRODUCTION

Mixing intravenous medications in the same infusion bag or in the same syringe is a common practice among health care providers in hospitals. This is due to multiple intravenous medications given to the patients, among other factors such as difficulties with venous access limiting the number of intravenous lines available for administration of multiple drugs However, mixing medications in continuous infusion is quite often done without an evidence-based decision regarding the compatibility of the admixture.[1]

Lack of supportive compatibility data when mixing medications may cause a tremendous effect on a patient's health. A multicenter, cross-sectional observational study concluded that the absence of supportive compatibility data, inappropriate combinations of drug infusions are being infused together through ay-site was responsible for 8.5% of all patients admitted to Canadian intensive care units.[2] The various clinical effects caused due to incompatibilities may ultimately cause tissue ischemia, hypoxia and impairment in the discharge of metabolic end products. Due to the reduction in the micro circulation, the major organs like lungs and liver functions are reduced and ultimately progress to multi-organ failure, leading to extremely high mortality.[3] In the literature, fatal pulmonary embolism was attributed to incompatible combinations of drug infusions.[4,5]

Intravenous incompatibilities can occur when two or more drugs are administered through a single IV line or given in a single solution, resulting in an undesirable reaction[3]. Incompatibility problems are more likely to arise when small concentrated volumes are mixed in a syringe rather than in the larger volume of an infusion bag, this is because of higher mutual drug concentrations and potentially greater pH changes in the more concentrated solution.[1] Generally, there are three common types of incompatibilities: physical, chemical and therapeutic incompatibility.[6] A physical incompatibility is also called a pharmaceutical incompatibility. Physical incompatibilities occur when one drug is mixed with other drugs or solutions to produce a product that is unsafe for administration.[7] On the other hand, chemical compatibility reflects the chemical degradation of one or more of the admixed drugs, resulting in toxicity or therapeutic inactivity.[1] The degradation is not always visible; the reaction of admixed drugs may result in alterations in either integrity or potency of the drug without visible change.[8] Non-visible chemical incompatibility may be detected only by analytical methods.[9] Therapeutic incompatibility occurs when two or more drugs, IV fluids or both are combined and the result is a response other than that intended, this occurs within the body of the patient.[7]

Non-steroidal anti-inflammatory drugs (NSAIDs) are widely used as mono therapy or in combination with other drugs to treat various diseases especially in pain management. Combining nonopioid analgesics of different classes has become an accepted method in reducing the doses of individual drugs, providing superior pain relief and reducing analgesic-related side effects.[10] Acetaminophen and ketoprofen combination is intended to get a synergistic effect in pain-relieving and fever reduction. Historically, intravenous acetaminophen was approved by the US Food and Drug Administration (FDA) since 2010.[11] It is common clinical practice in Mauritanian hospitals to mix intravenous

acetaminophen and ketoprofen together or each one with other drugs and IV fluid (sodium chloride 0.9%) with an absence of supportive compatibility data. In the shade of undocumented information, this review helps giving clear-cut answers about the compatibility of this admixture. Therefore, the current systematic review aims to assess the stability and compatibility of intravenous acetaminophen and ketoprofen admixture and to evaluate the quality of the data in these studies.

Table 1: Summary of the main characteristics of all included articles

Reference	Analytical method	Mobile phase composition and pH	Drugs dose used	Study duration	Conclusion
Bernard L *et al* ., 2011[16]	HPLC	Not reported	Acetaminophen 10 mg/mL Ketoprofen 1 mg/mL	24 hours	no drug instability or incompatibility appears during the study
Balayssac D *et all* ., 2009[17]	HPLC coupled to UV-975 detector	Acetonitrile/Water (70/30, v/v). -pH: phosphate buffer adjusted to pH 5	ketoprofen (1 mg/mL) in 100 ml Acetaminophen solution 1 g/100 mL acetaminophen	24 hours	Concentrations remained under the 5% variation compared with their initial value
Hamdi M. *et al*., 2009[18]	HPLC coupled to UV detector	Acetonitrile phosphate buffer pH of 2.0	Acetaminophen 1g/100 mL Ketoprofen 100 mg/2mL (to be dissolved in 200 ml isotonic saline prior I.V administration)	24 hours	The mixture in clinically relevant concentrations in isotonic saline and at room temperature are stable and compatible for at least 24 h
Kambia NK. *et al.,* 2006[19]	HPLC with linear photodiode array UV detector	Acetonitrile: aqueous buffer mixture (40/60, v/v) pH: 5.6	Ketoprofen 100 mg vial was diluted and added to acetaminophen 1 g/100 mL.	48 hours	Admixtures were physically compatible and chemically stable for up to 48 hrs at room temperature.
Navarro AA *et al.,* 2018[20]	HPLC		Dexketoprofen* 50 mg/ 2 ml acetaminophen 1000 mg/100 mL	20 days	The binary mixture in a low-density polyethylene bottle is stable for 5 days under refrigeration and 15 days at room temp.

Table 2: Quality assessment tool for physical compatibility

Quality Assessment parameter	References				
	Bernard L *et al*[16]	Balayssac D *et al*[17]	Hamidi M. *et al*[18]	Kambia N *et al*[19]	Navarro A *et al*[20]
1. Precipitate Formation	No	No	No	Yes *	No
2. Color Change of mixture	No	No	No	No	No
3. pH Change Over Time	No	No	Yes**	No	Yes**
4.Gas Production	No	No	No	No	No
5. Testing Done in triplicate	Yes	Yes	No	Not Reported	Yes
6. Reporting drugs diluents	Not Reported	Yes	Yes	Yes	Yes
7. Descripting study method	Yes	Yes	Yes	Yes	Yes

*: Binary mixture containing acetaminophen (100 mL) 1000 mg and dexketoprofen-trometamol (2 mL) 50 mg in a low-density polyethylene bottle is physicochemical stable for 5 days under refrigeration and 15 days at room temperature. **: slightly less than 1 unit change of pH.

Table 3: The quality assessment tool for chemical compatibility

Quality assessment parameter	References				
	Bernard L *et al*[16]	Balayssac D *et al*[17]	Hamidi M. *et al*[18]	Kambia N *et al*[19]	Navarro A *et al*[20]
1.Describing study materials	Yes[b,a]	Yes[a]	Yes[a]	Yes	Yes[a]
2.Describing testing conditions including temperature and light?	Yes	Yes	Yes	Yes	Yes
3.Including time zero analysis	Yes	Yes	Yes	Yes	Yes
4. Performing study in replicate?	Yes	Yes	No	Yes	Yes
5.Describing analytical methods	Yes	Yes	Yes	Yes	Yes

[*]**:** including drug concentrations, drug diluents, testing containers, drug manufacturers, and lot numbers
[a]: testing containers not reported. [b]: Drug diluents and lot numbers are missing

DISCUSSION

An electronic search was performed in using MEDLINE, HINARI, Google scholar and international peer-reviewed journals to identify all published research articles on the subject until April 2019. HINARI is a WHO program intended to enable developing countries to access with low or free cost to biomedical and health literature published in key databases such as Cochrane, CINAHL, and Scopus. The reference lists of selected studies were reviewed for additional relevant articles. The main search terms used were "compatibility and acetaminophen and ketoprofen", "stability and acetaminophen and ketoprofen", "Acetaminophen and ketoprofen in one syringe", "Acetaminophen and ketoprofen admixture", "Acetaminophen or acetaminophen and ketoprofen".

All original research articles published in the English language on the stability and/or physical and chemical compatibility of acetaminophen infusion admixed with ketoprofen beside explained study protocol were included. Studies on more than the binary mixture of ketoprofen and acetaminophen, a combination of a solid dosage form of ketoprofen and acetaminophen,

acetaminophen infusion admixed with other drugs, observational studies, and review articles were excluded.

Studies that met all eligibility criteria were subjected to further quality assessment analysis. Assessment tools for physical compatibility consisted of eight parameters, including evaluation of the followings; precipitate formation, color change, pH at time zero and over time, gas production, testing done in replicate, describing the drug diluents for all drugs and describing study methodology.[12] The quality data assessment tools for chemical compatibility studies consisted of eight parameters namely describing materials including drug concentrations, drug diluents, testing containers and drug manufacturers and lot numbers, describing testing conditions including temperature and light, describing analytical methods, conducting time zero analysis and performing assays in replicate.[12]

Only five articles met all inclusion criteria and were assessed. The main characteristics of these articles were summarized in Table 1. Included articles were published from 2006 to 2018. These studies have the same acceptance criteria defined by ICH guidelines.[13] These guidelines consider a 5% change in assay from its initial value, any degradation product exceeding acceptance criteria; failure to meet the acceptance criteria for appearance, physical attributes and functionality test; failure to meet the acceptance criterion for pH.

Admixture compatibility study of ketoprofen was performed with normal Saline (0.9% Sodium Chloride Injection USP), Glucose (5% Dextrose injection USP) and Ringer lactate solution (Lactate Ringer Solution USP) by Srikant Pimple *et al.*[14] and concluded compatibility of dexketoprofen with all used diluents.

Included studies did not report any information concerning acetaminophen degradation products. However, research carried by Catherine Curran reported that the acetaminophen (Perfalgan®) did not degrade on exposure to air over 24 hours, neither did it degrade on exposure to acid, alkali, oxidative or heat stress[15]. Also, the octanol: water partition coefficient likewise stayed constant.[15]

The studies duration was varied from 24 hours in three studies (60%),[16-18] 48 hours in one study (20%)[19] and even 20 days in one study (20%).[20] Out of five studies, only one study reported a loss > 10% of ketoprofen after 24 hours of stasis in the IV administration set, which was explained by the probability of interaction between ketoprofen and PVC infusion bag.[16] Interestingly, the stability of the ketoprofen enantiomer dexketoprofen and acetaminophen admixture over 20 days[20] may open a perspective for pre-mixed injection manufacturing in the future.

Regarding the instrument used for drugs analysis, all studies used high-performance liquid chromatography (HPLC) technique coupled. The HPLC was coupled to a UV detector in two studies[17, 18] and photodiode array detector in one study.[19] Two studies did not mention the type of detector used. The five studies described the drug dose used.

Findings of study quality assessment for physical and chemical compatibility were summarized in Tables 2 and 3 respectively. Concerning pH, none of the studies reported any pH change over time measured except one study[19] which demonstrate a slight decrease in pH over 48 hour and the changes in pH was about 0.96 pH unit. This phenomenon was justified by the author as a result of weak acid properties of ketoprofen. However, changes in pH do not affect the stability of the mixture over the studied period. While the testing condition has been described in all studies, the test was done in replicate only in one study[19] this will increase study precision. Drug diluents have been reported for all drugs studied, nonetheless, some studies used ready-to-use drugs. Study materials and analytical methods have been described or referenced in all selected studies. Although validation of stability-indicating analytical technique has not been described or referenced.

In addition, when mixing drugs taken from ampoules of sterile solutions, there is a potential issue of bacterial contamination. None of these studies examined admixed solutions for such contamination. Generally, to reduce contamination risk solutions that may support bacterial growth should not be prepared more than a few minutes in advance of their administration. Pre-mixed IV admixtures may become feasible and will reduce contamination.

CONCLUSION

Based on these reviewed studies, we can conclude that acetaminophen and ketoprofen admixture is stable and compatible showing neither loss of concentration nor degradation products over 24 to 48 hours concerned health authorities are recommended to support efforts aiming to ensure drugs admixtures stability and compatibility and supply hospitals with updated compatibility chart and clear guidelines showing admixture procedure and concentration of items to be admixed.

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