



# **Alteration in the Efficacy of in Vitro Vancomycin and Ceftazidime Prepared in Normal Saline Versus Balanced Salt Solution in the Management of Ocular Infections**

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## **Authors' contributions**

*This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.*

## **Article Information**

DOI: 10.9734/JPRI/2021/v33i53A33666

### Editor(s):

(1) Dr. Farzaneh Mohamadpour, University of Sistan and Baluchestan, Iran.

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Complete Peer review History, details of the editor(s), Reviewers and additional Reviewers are available in this link:

<https://www.sdiarticle5.com/review-history/76716>

**Review Article**

**Received 09 September 2021**

**Accepted 18 November 2021**

**Published 06 December 2021**

## **ABSTRACT**

**Objective:** The purpose of this review article is to highlight the efficacy of Vancomycin and Ceftazidime formulated in different solutions for ocular use in the management of microbiological Ocular infections varies.

**Methodology:** To locate and assess all relevant literature, we employed systematic review as a search approach, utilizing punctilious and unambiguous methodologies. We initiated by stipulating key terms and selecting appropriate databases for your literature search. To find replicable and reportable publications from high-quality peer-reviewed journals, we used Google Scholar, PubMed, and Research Gate.

**Results:** Ceftazidime precipitated at 37 degree Celsius, but not at room temperature, however it did not show any effect on the pH of the medium. In both the media of Normal Saline and Balanced Salt Solution, it precipitated on its own or when coupled with vancomycin. Ceftazidime was initially

prepared in Balanced Salt Solution rather than Normal Saline, which resulted in further precipitation. Ceftazidime prepared in Normal Saline precipitated to 54% after 168 hours in the dialysis chambers, compared to 88% in Balanced Salt Solution. Ceftazidime synthesized in Normal Saline declined from an initial concentration of 137.5 to 73.4 µg/ml after 48 hours, while ceftazidime prepared in Balanced Salt Solution decreased to 6.3µg/ml. Vancomycin precipitation was inappreciable.

**Conclusion:** Vancomycin did not precipitate in Normal Saline or Balanced Salt Solution, according to this systemic study. Regardless of the presence of vancomycin, ceftazidime precipitated, and it precipitated more expeditiously if it was produced in Balanced Salt Solution rather than Normal Saline.

*Keywords: Vancomycin; ceftazidime; effectiveness; normal saline; and balanced salt solution.*

## 1. INTRODUCTION

Pharmaceutical and medical sciences face significant hindrances in delivering ophthalmic drugs. For decades, scientists have worked to improve the current dose formulations [1-4]. Because eye disorders are strenuous to treat, ocular forms must be safe, non-allergic, and sterile. Ocular topical formulations are prescribed frequently in practice [5]. Tear fluid turnover, nasolacrimal drainage, the corneal epithelium, and blood-ocular barriers all reduce local drug bioavailability and ocular surface residence time in topical application [6]. Antibiotics delivered systemically and topically are thwarted by static and dynamic ocular barriers, which are part of the eye's natural defensive mechanisms [7]. Blepharitis, conjunctivitis, scleritis, keratitis, and dry eye syndrome are examples of anterior segment disorders that can be treated with topical or periocular medications [8,9]. Drug transport to the anterior and posterior segment of the eye for glaucoma, endophthalmitis, or uveitis, both have poor bioavailability and obstacles. Despite the potential of complications, intraocular administration may be recommended [10]. Many strategies have been developed to increase the drug's bioavailability, controlled release, and therapeutic impact [11].

Therapeutic delinquencies against various Micro organisms invading the eye with traditional regimens, as well as the emergence of resistant strains of these have necessitated the use of fortified antibiotic eye drops in subjects who do not respond to conventional treatment modalities, as is frequently the case in long-term care [12]. Due to the growing need for such therapies, multiple studies addressing the in vitro properties of fortified antibiotic eye drops have recently appeared in the literature. Antibiotics based on β-lactams (penicillins and cephalosporins) are not commercially attainable as eye drops because

they are relatively unstable in an aqueous solution [13-15]. Notwithstanding this, solutions suitable for topical treatment of bacterial eye infections can be made locally from intravenous preparations [16]. Different solutions, such as sterile water, normal saline, balanced salt solution, and Ringer's lactate, are used to make certain key antimicrobials.

## 2. VANCOMYCIN

### 2.1 Pharmacokinetics and Mechanism of Action

Vancomycin is a bactericidal drug that prevents the polymerization of peptidoglycan in cells, resulting in cell lysis [17]. Therapeutic vitreous vancomycin concentrations were only attained with intravitreal therapy, according to Ferencz et al. [18]. As observed in infected rabbit eyes, vancomycin has a half-life of 25 to 56 hours, with drug concentrations remaining above bactericidal levels for up to 72 hours [17].

### 2.2 Resistance and Activity Spectrum

Given the rising occurrence of βlactam antibiotic resistance, vancomycin has been the antibiotic of choice for coverage of gram-positive organisms [19]. Vancomycin is nearly 100 percent effective in the treatment of gram-positive ocular infections (including methicillin-resistant *Staphylococcus* species), but it has little effect on gram-negative pathogens [20]. Resistance to vancomycin is uncommon.

## 3. CEFTAZIDIME

### 3.1 Pharmacokinetics and Mechanism of Action

Ceftazidime is a third-generation cephalosporin that is effective against gram-negative bacteria

[21]. Ceftazidime is a bactericidal antibiotic that kills bacteria by crosslinking their cell walls with a trans peptidase enzyme. Ceftazidime has a half-life of 13.8 hours in phakic rabbit eyes [19].

### **3.2 Resistance and Activity Spectrum**

Ceftazidime, given at a dose of 2.25 mg/0.1 mL, has a broad therapeutic index and excellent in-vitro antibacterial activity [17]. Irvine et al. discovered that gram-negative ocular infection isolates were 100% sensitive to ceftazidime and 97% sensitive to amikacin [22]. In isolates with gram-negative endophthalmitis, ceftazidime sensitivities were higher than aminoglycoside sensitivities, according to a review [23]. Chances of bacterial resistance to ceftazidime varies.

## **4. MATERIALS AND METHODS**

### **4.1 Search Method**

To locate and assess all relevant literature, we employed systematic review as a search approach, utilizing punctilious and unambiguous methodologies. We initiated by stipulating key terms and selecting appropriate databases for your literature search. To find replicable and reportable publications from high-quality peer-reviewed journals, we used Google Scholar, PubMed, and Research Gate.

A manual literature search, snowballing, and obtaining expert advice were some of the other search tactics employed to find items of relevance.

### **4.2 Term(s) Used**

We searched for papers using terms such as “ceftazidime,” “vancomycin,” “intravitreal,” “Balanced Salt solution,” “Normal Saline,” and others.

The Boolean Operator ‘OR’ was employed to combine these phrases. To discover the most relevant studies, we acquired an iterative search method that combined multiple key phrases.

To boost the pertinence of the results and limit them down, the Boolean Operator ‘AND’ was employed.

### **4.3 The Following Studies were Chosen**

After a careful search and selection that included four processes, namely identification, screening, deciding eligibility, and final inclusion, the

comprehensive search generated over 11,100 articles, which were effectively filtered to three shortlisted articles [24,25,26].

### **4.4 Visual and pH Test (Study 1)**

A Standard mixture with solutions of 1 mg vancomycin and 2.2 mg ceftazidime in 0.1 mL of 0.9% Normal Saline or Balanced Salt Solution were mixed individually with 4 mL Normal Saline and Balanced Salt Solution for incubation at ambient temperature 37°C.

### **4.5 Checkerboard Analysis (Study 2)**

Mixture samples with various concentrations of ceftazidime and vancomycin prepared in Normal Saline or Balanced Salt Solution were incubated at 37°C in microtiter plates which were covered with paraffin foil. Aliquots were taken at 24 and 48 hours for assays by HPLC (ceftazidime) and fluorescence polarization (vancomycin) to determine the quantity of free drugs.

### **4.6 Study 3: Equilibrium Dialysis Control Experiment with NS as the Medium**

Equilibrium dialysis was done in a Spectrum Medical Industries, Los Angeles, CA, equilibrium dialyzer with a half-cell working volume of 5.0 mL vancomycin (625 g) and ceftazidime (1375 g) produced in NS [27]. Half-cell chamber A was filled with the mixes, which were separated from half-cell chamber B by a semipermeable dialysis membrane (Spectrapor; Medical Industries) with a molecular weight cutoff of 6000 to 8000. 5 mL NS was added to both chambers. At 37°C, the entire system was incubated. For antibiotic testing, aliquots were obtained from half-cell chamber B at appropriate time intervals up to 168 hours.

### **4.7 Study 4: Equilibrium Dialysis Control Experiment with BSS as the Medium**

The approach was the same as in Study 3, but in both chambers BSS was employed as the preparation medium.

## **5. DISCUSSION**

### **5.1 Visual and pH Test (Study 1)**

After a day of incubation at 37°C, precipitates were visible in Normal Saline and Balanced Salt Solution, but not at room temperature. There was

no change in pH of 7.2 prior to or after precipitation.

### 5.2 Checkerboard Analysis (study 2)

Vancomycin did not cause remarkable precipitation or a significant drop in Normal Saline after 24-48 hours. Due to precipitation of Ceftazidime, its concentration decreased indicating precipitation in the first column. However, there were no changes in vancomycin concentrations in combinations of ceftazidime and vancomycin after 48 hours, but an escalating reduction in ceftazidime (median, 26.8%; range 12.0%–39.7%), which suggested ceftazidime precipitation only. The amount of precipitation was measured by evaluating the decrease in antibiotic concentration.

In Balanced Salt Solution preparation after 48 hours, Vancomycin individually precipitated from 10.9 percent to 34.2 percent (median, 15.5 percent; first row) Ceftazidime resulted in significantly higher precipitation in Balanced Salt Solution as compared to Normal Saline. The median decrease after 48 hours was 94.9%(range, 93.7 percent–95.8 percent; first column). The amount of precipitation in the mixture was corresponding to what it would be if the antibiotics were used alone. Switching vancomycin concentrations in the Normal Saline and Balanced Salt Solution combinations did not appear to have a considerable affect on ceftazidime concentration.

### 5.3 Study 3: Equilibrium Dialysis Control Experiment with NS as the Medium

After approximately 60 hours, the vancomycin concentration in chamber B spiked to about 45 percent of the initial concentration in chamber A, then achieved a plateau, showing no decline until the experiment ended at 168 hours. After an initial crossing into chamber B for the first 20 hours, ceftazidime concentration dropped steadily to around 20% at 168 hours, indicating precipitation. The total amount of free vancomycin in chambers A and B after 168 hours was 591.1 g and free ceftazidime was 577.0 g, respectively, compared to the commencing levels of 625 and 1375 g. As a result, vancomycin was down 5.4 percent and ceftazidime was down 58.0 percent. Precipitation was thought to be the culprit in decreased concentration.

### 5.4 Study 4: Equilibrium Dialysis with BSS as the Medium

Vancomycin concentration in chamber B raised similar to study 3 in the first 60 hours. Following an initial crossover into chamber B in the first 10 hours, ceftazidime concentrations declined by more than 90% after 120 hours [28]. The aggregated amounts of free vancomycin in chambers A and B after 168 hours were 549.4 g and 244.2 g, respectively, in contrast to the starting values of 625 and 1375 g. Vancomycin and ceftazidime levels reduced by 12.1 percent and 82.0 percent, respectively, because of precipitation.

In a subsequent experiment using Balanced Salt Solution-prepared antibiotics, the vancomycin concentration in chamber B escalated to slightly more than 50% of the original concentration in chamber A following approximately 70 hours [29]. After an initial crossing into chamber B during the first 10 hours, the concentration of ceftazidime had dropped by more than 90% after 40 hours. After 168 hours, the total amount of free vancomycin in chambers A and B was 135.6 g, and the total quantity of ceftazidime was 34.5 g, compared to 125 g and 275 g, respectively, indicating no loss of vancomycin [30] but approximately 88 percent loss of ceftazidime. The concentration of free ceftazidime in dialysis chamber B was 6.3 g/mL after 48 hours.

The American Academy of Ophthalmology's preferred practice pattern guidelines recommend the use of sterile normal saline for compounding vancomycin [28]. However, a variety of other solvents have also been used. The differences in ionic composition, pH, and buffering capacity of these solvents can affect the physicochemical stability of vancomycin [31].

## 6. CONCLUSION

In our systemic review [32] Vancomycin did not precipitate in Normal Saline, Balanced Salt Solution. Even though the volume was small, ceftazidime precipitated regardless of the presence of vancomycin. It is speculated that mineral materials in the Balanced Salt Solution enhance the precipitation effects. As a result of the presence of potassium ions, calcium ions, glutathione, other reducing and oxidizing agents, precipitation was nimble when the ceftazidime preparation was introduced to [33] Balanced Salt Solution than when it was added to Normal Saline [34].

## DISCLAIMER

The products used for this research are commonly used products in our area of research and country. There is no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but only for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

## CONSENT

It is not applicable.

## ETHICAL APPROVAL

It is not applicable.

## COMPETING INTERESTS

Authors have declared that no competing interests exist.

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*Peer-review history:*  
The peer review history for this paper can be accessed here:  
<https://www.sdiarticle5.com/review-history/76716>