Review Article

Alteration in the efficacy of in Vitro Vancomycin and Ceftazidime prepared in Normal Saline versus BSS in the management of Ocular infections

ABSTRACT

OBJECTIVE: The purpose of this review article is to show how 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, employing rigorous and transparent methodologies. Begin by specifying 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 degrees C, but not at room temperature, and had no effect on the medium's ph. In all three media of NS, BSS, and vitreous, it precipitated on its own or when coupled with vancomycin. Ceftazidime was first prepared in BSS rather than NS, which resulted in more precipitation. Ceftazidime prepared in NS precipitated to 54 percent of that in vitreous after 168 hours in the dialysis chambers, compared to 88 percent in BSS. Ceftazidime synthesized in NS fell from an initial concentration of 137.5 to 73.4 microg/mL in vitreous medium after 48 hours, while ceftazidime prepared in BSS decreased to 6.3 microg/ml. Vancomycin precipitations was negligible

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 heavily if it was produced in BSS rather than NS.

KEYWORDS

Vancomycin, ceftazidime, effectiveness, normal saline, and balanced salt solution

Introduction:

Pharmaceutical and medical sciences face significant hurdles in delivering ophthalmic drugs. For decades, scientists have worked to improve the current dose formulations. Because eye disorders are difficult to treat, ocular forms must be safe, non-allergic, and sterile. 90 percent of the indicated formulation is in topical form [1]. 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. Antibiotics delivered systemically and topically are thwarted by static and dynamic ocular barriers, which are part of the eye's natural defensive mechanisms[2a]. Blepharitis, conjunctivitis, scleritis, keratitis, and dry eye syndrome are examples of anterior segment disorders that can be treated with topical or periocular medications. Drug transport to the posterior segment of the eye for glaucoma, endophthalmitis, or uveitis, and to the anterior segment for glaucoma, endophthalmitis, or uveitis, both have poor bioavailability and obstacles. Despite the potential of complications, intraocular administration may be recommended [2].Approaches has been developed to increase the drug's bioavailability, controlled release, and therapeutic impact [3].

Therapeutic failures to treat Pseudomonas aeruginosa and Staphylococcus aureus infections of the eye with traditional regimens, as well as the emergence of resistant strains of these bacteria, 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 (Lemming 1999; Robinson et al. 1999; Hvding 2008).Due to the growing need for such therapies, a number of research addressing the in vitro properties of fortified antibiotic eye drops have recently appeared in the literature (Arc et al. 1999; Barnes & Nash1999). Antibiotics based on b-lactams (penicillins and cephalosporins) are not commercially accessible as eye drops because they are relatively unstable in aqueous solution [4]. Despite this, solutions suitable for topical treatment of bacterial eye infections can be made locally from intravenous preparations. Different solutions, such as sterile water, normal saline, balanced salt solution, and Ringer's lactate, are used to make certain key antimicrobials.

Vancomycin

Pharmacokinetics and Mechanism of Action

Vancomycin is a bactericidal drug that prevents the polymerization of peptidoglycan in cells, resulting in cell lysis[5]. Therapeutic vitreous vancomycin concentrations were only attained with intravitreal therapy, according to Ferencz et al. [6]. As observed in infected rabbit eyes, vancomycin has a half-life in the vitreous of 25 to 56 hours, with drug concentrations remaining above bactericidal levels for up to 72 hours.(7) and (8)

Resistance and Activity Spectrum

Given the rising occurrence of -lactam antibiotic resistance, vancomycin has been the antibiotic of choice for coverage of gram-positive organisms[5]. 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 [9]. Resistance to vancomycin is uncommon.

Ceftazidime:

Pharmacokinetics and Mechanism of Action

Ceftazidime is a third-generation cephalosporin that is effective against gram-negative bacteria such as Pseudomonas aeruginosa. 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 [10].

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 [11, 12, 17]. Irvine et al. discovered that gram-negative ocular infection isolates were 100% sensitive to ceftazidime and 97 percent sensitive to amikacin [13]. In isolates with gram-negative endophthalmitis, ceftazidime sensitivities were higher than aminoglycoside sensitivities, according to a review [14].There’s a chance that bacterial resistance to ceftazidime varies. [5]

MATERIALS AND METHODS:

Search Method: To locate and assess all relevant literature, we employed systematic review as a search strategy, employing rigorous and transparent methods. Begin by specifying key terms and selecting appropriate databases for your literature search. We found replicable and reportable publications from high-quality peer-reviewed journals using Google Scholar, PubMed, and Research Gate [15]. Only the English language was used in the articles.

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

Term(s) used:

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

The search was maintained broad in order to cover the entire breadth of the subject. The Boolean Operator ‘OR’ was employed to combine these phrases. To discover the most relevant studies, we employed an iterative search method that combined multiple key phrases.

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

The following studies were chosen: After a careful search and selection process 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.

(Author Alvin K. H. Kwok’s original article appeared in Investigative Ophthalmology & Visual Science, April 2002, Vol.43, 1182-1188.

Visual and pH Test (Study 1)

A standard mixture of 2.2 mg ceftazidime and one milligram vancomycin in 0.1 mL of 0.9 percent NS or Balanced Salt Solution had been mixed one at a time with four mL NS, BSS, or vitreous for incubation at room temperature or at 37°C.

Checkerboard Analysis (Study 2)

In microtiter plates coated with paraffin foil, mixture samples containing varying concentrations of ceftazidime and vancomycin were incubated at 37°C with varied concentrations of ceftazidime and vancomycin produced in NS or BSS. To measure the amount of free medicines, aliquots were collected at 24 and 48 hours for HPLC (ceftazidime) and fluorescence polarization (vancomycin) assays[16].

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[18].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.

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.

Discussion and Conclusions:

Visual and pH Test (Study 1)

Precipitate was visible in NS and BSS after 1 day of incubation at 37°C, but not at room temperature. The pH of 7.2 did not change before or after precipitation.

Checkerboard Analysis (study 2)

Vancomycin did not cause visual precipitation or a meaningful drop in NS after 24 or 48 hours. The concentration of ceftazidime alone decreased from 0% to 24.7 percent, indicating precipitation within the first column. There were no changes in vancomycin concentrations in combinations of ceftazidime and vancomycin after 48 hours, but a progressive reduction in ceftazidime (median, 26.8%; range 12.0%–39.7%), indicating ceftazidime precipitation but not vancomycin precipitation. The amount of precipitation was measured by the decrease in antibiotic concentration.

Vancomycin alone precipitated from 10.9 percent to 34.2 percent in BSS preparation after 48 hours (median, 15.5 percent; first row). In BSS, ceftazidime alone resulted in much higher precipitation than in NS. The median decrease after 48 hours was 94.9 percent (range, 93.7 percent–95.8 percent; first column).The amount of precipitation in the mixture was similar to

what it would be if the antibiotics were used alone. Changing vancomycin concentrations in the NS and BSS combinations did not appear to affect ceftazidime concentration.

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

After around 60 hours, the vancomycin concentration in chamber B climbed 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 beginning levels of 625 and 1375 g. As a result, vancomycin was down 5.4 percent and ceftazidime was down 58.0 percent. Precipitation was blamed for the decline.

Study 4: Equilibrium Dialysis with BSS as the Medium

Vancomycin concentration in chamber B increased in the first 60 hours, similar to study 3. After an initial crossover into chamber B in the first 10 hours, ceftazidime concentrations dropped by more than 90% after 120 hours[19].The total amounts of free vancomycin in chambers A and B after 168 hours were 549.4 g and 244.2 g, respectively, compared to the starting values of 625 and 1375 g. Vancomycin and ceftazidime levels dropped by 12.1 percent and 82.0 percent, respectively, due to precipitation.

In a subsequent experiment using BSS-prepared antibiotics, the vancomycin concentration in chamber B grew to slightly more than 50% of the original concentration in chamber A after approximately 70 hours.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 amount of ceftazidime was 34.5 g, compared to 125 g and 275 g, respectively, indicating no loss of vancomycin but approximately 88 percent loss of ceftazidime. The concentration of free ceftazidime in dialysis chamber B was 6.3 g/mL after 48 hours.

Conclusion:

Vancomycin did not precipitate in NS, BSS, or vitreous in our systemic review. Even though the volume was small, ceftazidime precipitated regardless of the presence of vancomycin, and it precipitated more extensively if it was prepared in BSS rather than NS. This suggests that mineral materials in the BSS have effective enhancing precipitation effects. Because of the presence of potassium ions, calcium ions, glutathione, and other reducing and oxidizing agents, precipitation was faster when the ceftazidime preparation was introduced to[20] BSS than when it was added to NS[21].

COMPETING INTERESTS DISCLAIMER:

Authors have declared that no competing interests exist. The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely 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 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.

References:

1. Gan, L.; Wang, J.; Jiang, M.; Bartlett, H.; Ouyang, D.; Eperjesi, F.; Liu, J.; Gan, Y. Recent advances in topical ophthalmic drug delivery with lipid-based nanocarriers. *Drug Discov. Today***2013**, *18*, 290–297. [**Google Scholar**] [**CrossRef**] [**PubMed**]
2. Le Bourlais, C.; Acar, L.; Zia, H.; Sado, P.A.; Needham, T.; Leverge, R. Ophthalmic drug delivery systems—Recent advances. *Prog. Retin. Eye Res.***1998**, *17*, 33–58. [**Google Scholar**] [**CrossRef**].

   2a https://joii-journal.springeropen.com/articles/10.1186/s12348-014-0022-z
3. Yellepeddi, V.K.; Palakurthi, S. Recent advances in topical ocular drug delivery. *J. Ocul. Pharmacol. Ther. Off. J. Assoc. Ocul. Pharmacol. Ther.***2016**, *32*, 67–82. [**Google Scholar**] [**CrossRef**] [**PubMed**]
4. https://onlinelibrary.wiley.com/doi/10.1111/j.1755-3768.2008.01306.x
5. https://www.researchgate.net/publication/329385014_A_Review_of_Antimicrobial_Therapy_for_Infectious_Uveitis_of_the_Posterior_Segment
6. Ferencz JR, Assia EI, Diamantstein L, Rubinstein E Vancomycin concentration in the vitreous after intravenous and intravitreal administration for postoperative endophthalmitis. Archives of ophthalmology. 1999;117(8):1023-7
7. Aguilar HE, Meredith TA, el-Massry A, Shaarawy A, Kincaid M, Dick J, et al. Vancomycin levels after intravitreal injection. Effects of inflammation and surgery. Retina.1995;15(5):428-32. pmid: 8594637
8. Park SS, Vallar RV, Hong CH, von Gunten S, Ruoff K, D'Amico DJ. Intravitreal dexamethasone effect on intravitrealvancomycin elimination in endophthalmitis. Arch Ophthalmol. 1999;117(8):1058-62
   https://www.researchgate.net/deref/file%3A%2F%2FC%3A%2FUsers%2Frain%2Downloads%2Fwww.ncbi.nlm.nih.gov%2Fpubmed%2F10448749
9. Benz MS, Scott IU, Flynn HW, Unonius N, Miller D.Endophthalmitis isolates and antibiotic sensitivities: a 6-year review of culture-proven cases. American journal of ophthalmology. 2004;137(1):38-42.
10. Shaarawy A, Meredith TA, Kincaid M, Dick J, Aguilar E,Ritchie DJ, et al. Intraocular injection of ceftazidime. Effects of inflammation and surgery. Retina. 1995;15(5):433-8 pmid: 8594638
11. Mochizuki K, Yamashita Y, Torisaki M, Komatsu M,Tanahashi T, Kawasaki K. Intraocular kinetics of ceftazidime(Modacin). Ophthalmic research. 1992;24(3):150-4.
12. Roth DB, Flynn HW. Antibiotic selection in the treatment of endophthalmitis: the significance of drug combinations and synergy. Survey of ophthalmology. 1997;41(5):395-401.
13. Irvine WD, Flynn HW, Miller D, PflugfelderSC.Endophthalmitis caused by gram-negative organisms.Archives of ophthalmology. 1992;110(10):1450-4.Med Hypothesis DiscovInnovOphthalmol. 2018; 7(4)153 ANTIMICROBIAL THERAPY FOR INFECTIOUS UVEITIS
14. Chamberland S, L'Ecuyer J, Lessard C, Bernier M,Provencher P, Bergeron MG. Antibiotic susceptibility profiles of 941 gram-negative bacteria isolated from septicemic patients throughout Canada. The Canadian Study Group. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America.1992;15(4):615-28
15. https://scholar.google.com.pk/scholar?start=40&q=efficacy+of+vancomycin+ceftazidime+and+amikacin+in+different+ophthalmic+solutions&hl=en&as_sdt=0,5&as_vis=1#d=gs_qabs&u=%23p%3DDZhoks0PLNgJ
16. https://www.karger.com/Article/Abstract/76111
17. https://pubmed.ncbi.nlm.nih.gov/18700884/
18. https://www.semanticscholar.org/paper/Stability-of-vancomycin-in-an-extemporaneously-Fuhrman-Stroman/439a8fba3ac7f8fe5c27ad3b48253968702b3b6f

19. https://pubmed.ncbi.nlm.nih.gov/20796261/
20. https://www.sciencedirect.com/topics/veterinary-science-and-veterinary-medicine/vitreous-humour#:~:text=Vitreous%20humor%20is%20the%20fluid,Scott%20and%20Oliver%2C%202001).
21. https://www.healthline.com/health/sodium-chloride