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RESEARCH ARTICLE
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INTRACAMERAL CEFUROXIME INDUCED RETINAL INFARCTION IN POST-OPERATIVE CATARACT SURGERY - A DISPROPORTIONALITY ANALYSIS IN FOOD AND DRUG ADMINISTRATION ADVERSE EVENT REPORTING SYSTEM DATABASE

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ABSTRACT

OBJECTIVES: During intraocular surgery, cefuroxime is frequently used to prevent post-operative endophthalmitis. Retinal infarction is a possible adverse reaction to its intracameral administration. Retinal infarction is the loss of visual acuity or a part of retina because of interruption of blood flow in retina. This study aims to evaluate the potential association between intracameral cefuroxime and retinal infarction by reviewing case studies and conducting a disproportionality analysis of spontaneous reports.

METHODS: A retrospective case/non-case study was conducted using spontaneous reports from the Food and Drug Administration Adverse Event Reporting System (FAERS). Disproportionality analysis was performed by calculating the Proportional Reporting Ratio (PRR), Reporting Odds Ratio (ROR), Relative Risk Reduction (RRR) and Chi Square test.

RESULTS: A total of 43 spontaneous reports of retinal infarction suspected to be caused by intracameral cefuroxime were identified from FAERS database. Through the disproportionate analysis of FAERS data, a signal was identified between retinal infarction and intracameral cefuroxime having ROR of 489.674 (333.052; 719.948), PRR of 486.907 (331.741; 714.651), RRR 383.456 (263.576; 557.86) and Chi-squared value is 12215.552 values respectively showing a positive signal.

CONCLUSION: The current investigation indicated that intracameral cefuroxime may increase the incidence of retinal infarction. It is essential to fully evaluate the situation and to take steps to prevent or mitigate the risk.

KEYWORDS: Intracameral Cefuroxime, Retinal Infarction, Cataract Surgery, FAERS.

INTRODUCTION

Drugs are a double-edged weapon because, despite being created specifically to treat disease, they can also have unintended side effects. It is very difficult to fully comprehend the drug's activity, whether desired or undesirable, and it will be impossible to find all adverse drug reactions (ADRs) throughout the drug development process due to the inadequacy of the research population. A drug's long-term effects might not become apparent for years after first using it, or it might take generations to fully comprehend a drug's properties.

The World Health Organization (WHO) describes the signal as "reported information on a potential causal association between an adverse event and a medicine, of which the relationship is unknown or has not been fully documented previously." Depending on the incident's severity and the information's accuracy, more than one report is typically needed to generate a signal. In pharmacovigilance, signal detection is a contemporary technique for identifying a drug's novel reaction. Although clinical trials and post-marketing observational studies are helpful in finding an ADR, they have many drawbacks. It is insufficient to extrapolate the safety of people from testing on animals.

Compared to the population of drug users, clinical trial participants or volunteers are few. The main limitations of traditional ADR identification techniques are restricted patient diversity, inadequate follow-up, and difficulties extrapolating short-term findings into long-term effects. Meanwhile, the execution of ADR signal detection without prior screening becomes incredibly time-consuming and ineffective due to the sharply increased ADR reports. Data Mining Algorithms (DMAs), also known as computer-assisted techniques for signal detection, have rapidly grown in recent years.[1]

Retinal Infarction

A retinal infraction is an acute painless and persistent monocular loss of visual acuity or a section of the retina. The most common cause of retinal arterial ischemia is an embolus from a distant source, like anterior circulation cerebral infarctions. Retinal emboli most commonly originate from the ipsilateral carotid artery, followed by the aortic arch and the heart. Drug-induced retinal infarction is uncommon, but it’s rarely seen in intracameral administration of cefuroxime when it's used as prophylaxis for endophthalmitis in cataract surgery.

A cataract is a cloudy lens. The lens is positioned behind the coloured part of your eye (iris). The lens focuses light that passes into your eye, producing clear, sharp images on the retina - the light-sensitive membrane in the eye that functions like the film in a camera. In cataract surgery, the cloudy lens is removed.

Endophthalmitis means bacterial or fungal infection inside the eye, involving the vitreous and/or aqueous humour. Most cases of endophthalmitis are exogenous, and organisms are introduced into the eye via trauma, surgery, or an infected cornea. Cataract surgery is one of the most common eye operations performed worldwide and endophthalmitis is commonly seen after this surgery because of the invasion of the globe by microbial flora, bacteria or fungi from the adnexa and environment during the time of surgery. So, the primary goal is to prevent this. Therefore, intracameral cefuroxime is given as prophylaxis in order to prevent endophthalmitis post-cataract surgery.[2]

Cefuroxime is a second-generation beta-lactam antibacterial cephalosporin, its primary inhibitory target is a penicillin-binding protein (PBP) 3, although it also inhibits PBP1a and PBP1b. The inhibition of PBP by cefuroxime blocks peptidoglycan synthesis and cell wall production, eventually resulting in bacterial lysis. Cefuroxime is used to treat bacterial infections like otitis media, uncomplicated gonorrhoea, impetigo, lyme disease, pharyngitis, tonsillitis, and uncomplicated urinary tract infection. Frequently observed side effects with cefuroxime are diarrhoea, nausea, vomiting, and vaginitis and it is also associated with some serious adverse effects such as erythema multiforme, steven-johnson syndrome, toxic epidermal necrolysis, anaphylaxis, and hypersensitivity reaction.[3]

First cefuroxime intracameral injection was developed in the European Union for prophylaxis of postoperative endophthalmitis after cataract surgery, each of the vial contents of 50 mg of

cefuroxime powder, which is reconstituted with 5 ml of sterile sodium chloride 0.9 % solution for injection. 0.1 ml of the reconstituted solution is administered to the patient by intracameral injection.[4]

Therefore, this commonly used intracameral cefuroxime injection used as prophylaxis for the management of endophthalmitis after cataract surgery has caused retinal infarction which has not been reported, hence we are attempting to find a correlation between intracameral cefuroxime induced retinal infraction in post-operative cataract surgery. Our study was conducted to identify the signal (intracameral infarction) of intracameral cefuroxime by disproportionality analysis in the FDA database using DMA.

MATERIALS AND METHODS

Data Source

The FAERS Public Dashboard is a user-friendly web-based tool for querying signal or Post Market Surveillance (PMS) data. It is used to collect data on drugs associated with osteomyelitis. It contains information on adverse events and medication error reports that have been voluntarily reported to the FDA by healthcare professionals, manufacturers, and patients. FAERS data includes information about the drug and the reaction (name of the drug, route of administration, outcome and the active ingredient). The database is intended to aid the FDA's post-market medication and therapeutic biologic product safety surveillance programme.

Study Design

It is a retrospective case-noncase which includes the analysis of a spontaneous reporting database. Retinal infarction was selected as the preferred event and the patients who had the adverse event were considered as cases.

Drug Selection

The drug list was derived from the open FDA Database and platform. Each drug was identified in FAERS by generic and brand names listed in the FDA Database and Drugs with greater than 15 reports were included in the study. FDA label, Medscape, Daily Med and Micromedex were used to check whether this drug is previously associated with retinal infarction. Later it was used for signal generation by disproportionality methods.

Inclusion Criteria

All reports of retinal infarction as an adverse event.

Exclusion Criteria

Reports that have cefuroxime as other than the primary suspect.

Statistical Analysis

The primary goal of disproportionality analysis is to create hypotheses about possible causal relationships between drugs and adverse effects. This was done with the use of the Proportional Reporting Ratio (PRR) and Reporting Odds Ratio (ROR) along with a 95% Confidence Interval to determine whether intracameral cefuroxime had a high probability of causing retinal infarction in the database, This helps to confirm (or not) whether there is any potential association.

The proportion of spontaneous reports for a given drug that is associated with a specific adverse outcome, divided by the corresponding proportion for all or several other drugs, is known as the proportional reporting ratio (PRR). It is used to measure the strength of the association between a drug and a specific adverse event. The PRR allows for a comparison of reporting frequencies to see if a specific adverse event with a specific drug is reported disproportionately compared to other adverse events and drugs. It can be calculated using the formula:

	Drug of Interest	**Other Drugs**
Event of Interest	A	B
Other Events	C	D
Table 1: Method for calculating PRR of the signal		

$$\boldsymbol{PRR = \frac{A(A+C)}{B(B+D)}}$$

The Reporting Odds Ratio (ROR) the odds of a certain event occurring with a drug, compared to the odds of the same event occurring with all other drugs in the database.

	Drug of Interest	**Other Drugs**
Event of Interest	A	B
Other Events	C	D
Table 2: Method for calculating ROR of the signal		

$$\boldsymbol{ROR = \frac{A/B}{C/D}}$$

In order to evaluate whether there are differences between categorical variables from a random sample, the statistical test known as chi-square is used.

$$\textbf{Chi-square} = \frac{(ad-bc)^2\ (a+b+c+d)}{(a+b)(c+d)(a+c)(b+d)}$$

Where,
"a" is the number of reports with adverse events of interest of the drugs of interest.
"b" is the number of reports with adverse events of interest of all other drugs.
"c" is the number of reports with all other adverse events of the drugs of interest.
"d" is the number of reports with all other adverse events of all other drugs.

Study Procedure

The publicly available FAERS database was downloaded from the FAERS website (http://h2876314.stratoserver.net:8080/OV2/search/) text file was extracted into an excel worksheet for further analysis. As the first step, the case IDs of the primary suspect reports of intracameral cefuroxime were isolated from the drug file in the database. A minimum of five adverse event reports were requisite to consider a DEC as clinically relevant. The same was selected for further analysis which resulted in 14 clinically relevant DECs (19 DECs were excluded as the route of administration was not intraocular). The obtained values were then applied for the computation of ROR and PRR. The results were compared with the preassigned threshold value, all the values above the threshold were considered as a positive signal. Those DECs which failed to show a positive signal were removed from the study.

RESULTS

During the study period, i.e. from the time of approval of intracameral Cefuroxime has been approved since 2012 by the European Medicines Agency and the French Agency of Drugs and Off-Label FDA use for Post-operative Cataract surgery to the date the FAERS database was accessed, on 23rd January 2023 the FAERS database had received 225 reports for retinal infraction.

	Cefuroxime	**All other Drugs**	**Sum Total**
Retinal infarction	43	182	225
All other AE	5652	25,383,857	25,389,509
Sum Total	5695	25,384,039	25,389.734
Table 3: Retinal Infarction associated with cefuroxime			

A positive signal for retinal infarction with intracameral cefuroxime with a signal strength of ROR of 489.674 (333.052; 719.948), PRR of 486.907 (331.741; 714.651), RRR 383.456 (263.576; 557.86) and Chi-squared value is 12215.552 was found. There are no concomitant drugs so background correction was not done. However, a positive signal was still present.

DISCUSSION

In this study we aimed to quantify the risk of retinal infarction occurring in patients receiving intracameral cefuroxime, through reviewing data from the FAERS database that has been queried with Open Vigil 2.1. Our analysis of the data revealed a positive signal with a signal strength of ROR of 489.674 in data. The increased association in our study, provides scope for further research/post marketing surveillance and can be used to generate hypotheses.

Subset Analysis

The total number of reported ADR of retinal infraction is 225 out of which cefuroxime induced retinal infarction is 43 and after background correction 27 were males, 5 females and in 11 cases gender was not specified.

Subset		**Cefuroxime**	**All other Drugs**	**Sum Total**
Males	**Retinal Infarction**	27	74	101
Females		5	95	100
Non specified		11	13	24

Table 4: Subset Analysis (Gender)

As a prophylactic treatment against infectious endophthalmitis, one milligram (1.0 mg) of intracameral cefuroxime has been suggested and is quickly evolving into the norm of treatment. There have been several published investigations on the safety of intracameral cefuroxime. Concern over cefuroxime's harmful effects on the human retina is currently on the rise. Although it is becoming more frequent, ocular toxicity caused by accidental intracameral injection of a cefuroxime overdose is not particularly prevalent. There have been documented clinical accounts of ocular toxicity brought on by an accidental intracameral cefuroxime.

Suleyman et al, conducted a retrospective case series study which included four patients and developed retinal or optic nerve infarction. In this study patients whose age was 80,70,60,75 years respectively and they were administered with intracameral cefuroxime dosed 70,60,50,60 mg respectively post-surgery and all the patients had complaints of lack of vision, hemorrhage in peripapillary, macular and inferior retinal regions.[5]

A case report of 70 year old women who underwent cataract surgery was given with 62.5 mg of intracameral cefuroxime developed single dot haemorrhage. Another case report of 60 year old patient presented with decreased vision after cataract surgery, this is because of the administration cefuroxime into the anterior chamber of eye.[6]

A study conducted by James E. Neffendorf et al., discovered that small eyes with a tamponade and an estimated ocular volume of 4 ml are especially vulnerable to cefuroxime toxicity after subconjunctival administration because any sclerotomy leak results in a vitreous concentration above the anticipated safe concentration of 7.69 mg/ml. On the other hand, they also discovered that toxicity from a 1 mg intracameral dose in the same eyes would be rare.[7]

The degree of cefuroxime toxicity's clinical symptoms varies from case to case and is correlated with both surgical difficulties and drug concentration. The suggested dose injection may induce a moderate, temporary, and treatable retinal toxicity in simple circumstances, however high-dose exposure might result in serious problems such macular infarction. Additionally, after receiving a cefuroxime injection, more serious consequences include widespread retinal edema, haemorrhage, diffuse capillary loss, and optic nerve atrophy may manifest.

This is because in serious cases, the lens capsule barrier that would have prevented medication transport to the posterior segment gets disrupted. Clinical characteristics in the current instance may have been more severe due to posterior capsule rupture, direct drug exposure to the retina, or toxicity-related blood-retinal barrier disruption.[8,9,10]

CONCLUSION

To avoid the emergence of serious problems linked to drug toxicity, surgeons and personnel should appropriately modify the intracameral medication dosage in difficult cataract procedures. In conclusion, at the approved cefuroxime concentration, retinal toxicity may manifest in challenging instances. Despite receiving high dose anti-inflammatory medication, the visual result appears to be poor. Therefore, health care professionals should adjust the intracameral drug dose accordingly in complicated cataract surgeries to prevent the development of severe complications related to drug toxicity. In conclusion, retinal toxicity may develop in complicated cases with the recommended cefuroxime concentration. Visual outcome seems to be poor despite high dose anti-inflammatory treatment.

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