Ocular Pharmacokinetics and Clinical Outcomes of Once Daily and Twice Daily Dosing of Topical Bromfenac Sodium 0.09% after Phacoemulsification

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I have no financial interests or relationships to disclose

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From Darkness to Light

Background & Aim of Study

Topical non-steroidal anti-inflammatory drugs (NSAIDs) are cyclooxygenase (COX) inhibitors- FDA approved for the prevention of intraoperative miosis and pain during cataract surgery as well as reduction of postoperative inflammation

Bromfenac 0.09% is associated with better ocular penetration, superior clinical efficacy and less increase in retinal thickness than nepafenac 0.03%

Rationale

- Bromfenac may be administered either once-daily or twice daily; however, clinical efficacy of different dosing regimens in phacoemulsification have not been adequately evaluated
- No study has evaluated the human aqueous pharmacokinetics after instillation of topical bromfenac 0.09%.

Aim

To evaluate the aqueous pharmacokinetics and clinical outcomes after instillation of once-daily and twice-daily topical bromfenac 0.09%

Methodology

Study Design

- **Prospective Interventional** Study

Setting

- Dr R. P. Centre for Ophthalmic Sciences, All India Institute of Medical Sciences, New Delhi, India

Methods

- **105 eyes** (one eye per patient) with immature senile cataract undergoing phacoemulsification
- Ocular co-morbidities/ prior ocular surgeries- excluded

Primary Outcome Measure

- Aqueous pharmacokinetics of topical bromfenac 0.09%.

Secondary Outcome Measures

- **Intraoperative miosis**
- **Postoperative pain**- assessed using visual analogue scale ranging from 0 to 10
- **Anterior chamber inflammation**- measured in terms of Summed Ocular Inflammation Score (SOIS) and AC flare .
  - *AC flare* assessed by flaremeter (FM- 600).
  - *SOIS* calculated by adding subject's AC cells and Flare grades with a range of 0 (minimum) to 8 (maximum)
- **Cystoid Macular Edema (CME)-** Central macular thickness and total macular volume estimated using Spectral domain-OCT

Methodology

Study Conducted in Two Phases

Phase I- Single-drop Aqueous Pharmacokinetics of Topical Bromfenac 0.09%

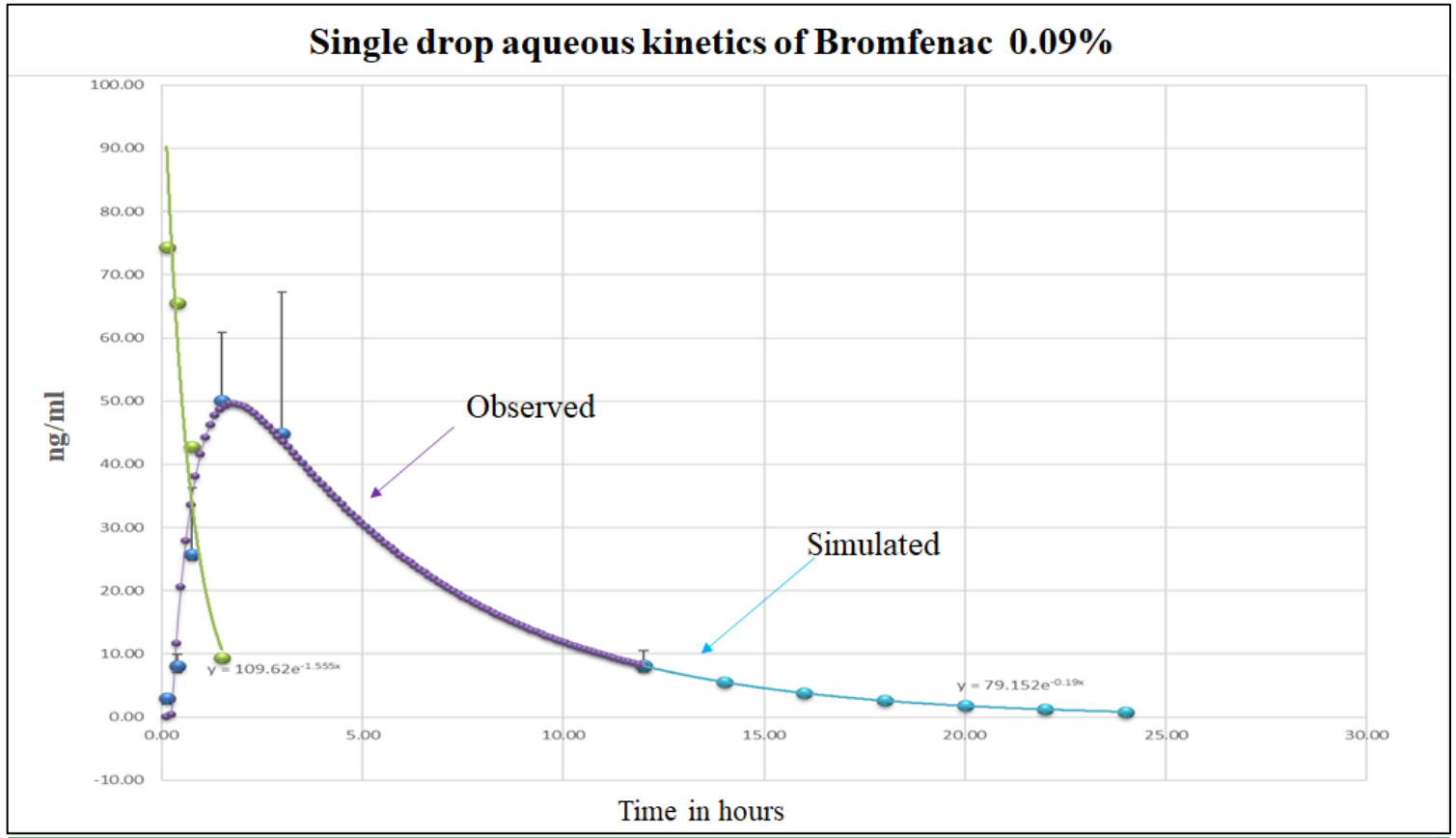
- **60 eyes of 60 patients** (10 eyes at each time point)
- Single drop of topical bromfenac instilled at variable time intervals of 15 minutes, 30 minutes, 1 hour, 2 hours, 4 hours and 12 hours before the surgery.
- Aqueous humor (0.1ml) was obtained using 30 G cannula mounted on a tuberculin syringe and the sample was stored at -80o C.
- Aqueous analysis was performed using Liquid Chromatography Mass Spectrometry (LC-MS/MS)

Phase II: Aqueous Concentration and Clinical Outcomes of Once Daily and Twice Daily Bromfenac 0.09%

- **45 eyes of 45 patients** undergoing phacoemulsification were divided into 3 groups
  - Control group (n=15) with no topical bromfenac
  - Once daily (OD) group (n=14) with topical bromfenac instilled once daily at 9 pm
  - Twice daily (BD) group (n=16) with topical bromfenac instilled twice daily at 9 am and 9 pm
- Topical bromfenac was instilled in OD and BD groups preoperatively for 5 days and continued till 3 months postoperatively.

Follow up was performed on day 1, day 7, 1 and 3 months postoperatively

Single Drop Aqueous Pharmacokinetics

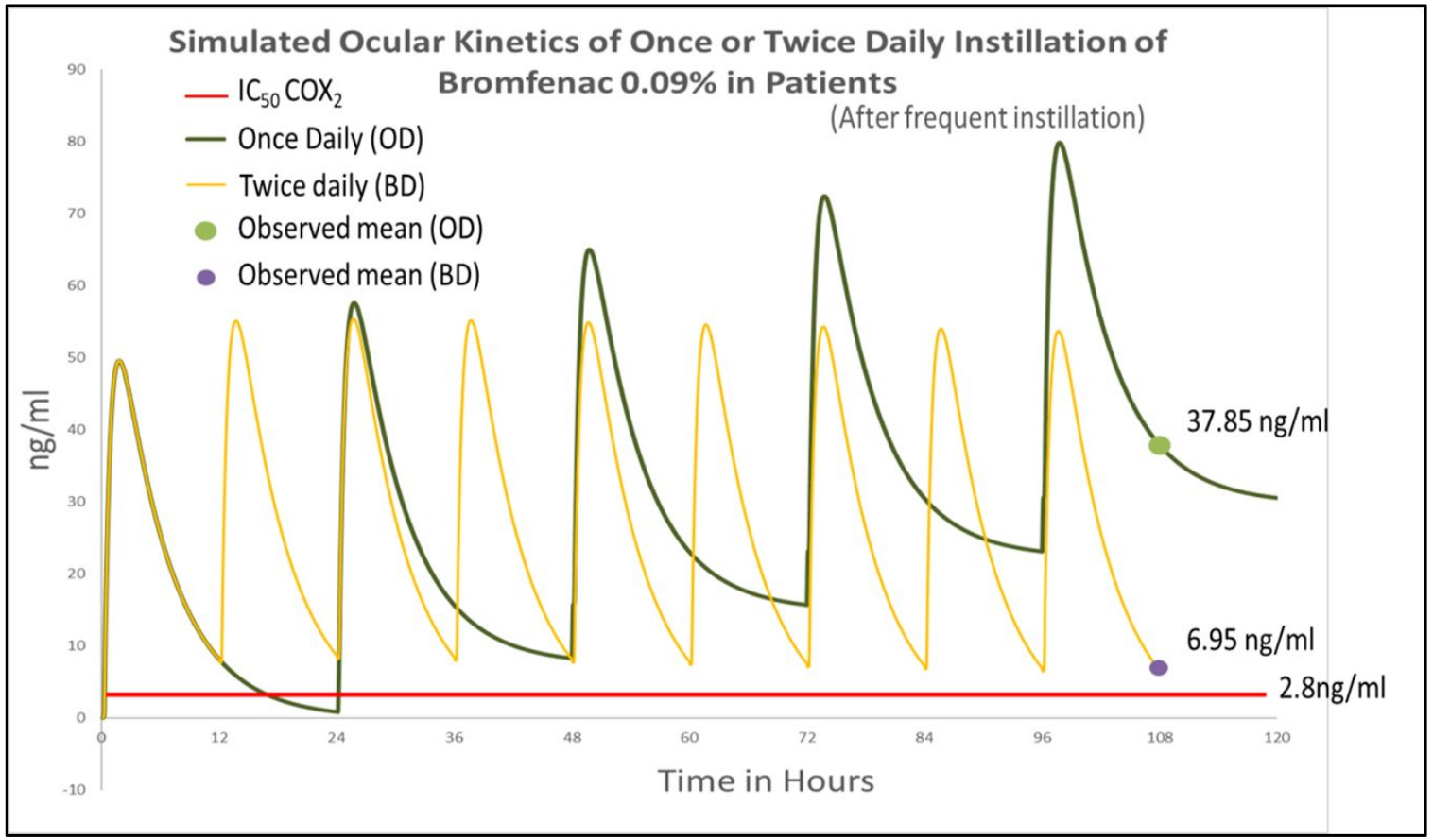


Time Interval	Aqueous Concentration (ng/ml)
15 minutes	2.99
30 minutes	8.04
1 hour	25.76
2 hours	63.73
4 hours	44.82
12 hours	8.14

Single Drop Aqueous Pharmacokinetics

- **Peak concentration- 63.73 ng/ml achieved (at 2 hours)**
- Aqueous half- life- 3.647 hours
- Mean residence time- 5.537 hours
- Absorption constant (K_a)- 1.555 hours
- Elimination constant (K_e)- 0.19 hours

OD vs BD Simulated Aqueous Pharmacokinetics



The minimum inhibitory concentration (IC_{50}) value of COX-2 inhibitors for humans is **2.8 ng/ml***

**Kida T, Kozai S, Takahashi H, Isaka M, Tokushige H, Sakamoto T. Pharmacokinetics and Efficacy of Topically Applied Nonsteroidal Anti-Inflammatory Drugs in Retinochoroidal Tissues in Rabbits. PLOS ONE. 2014 May 5;9(5):e96481.*

OD vs BD Aqueous Pharmacokinetics

Once-daily dosing- Mean aqueous bromfenac conc. **37.85 ng/ml**

Simulated kinetics showed a cumulative effect, minimum aqueous concentration of bromfenac at trough was less than IC_{50} after 1st dose

Twice daily dosing- Mean aqueous bromfenac conc. **6.95 ng/ml**

Consistent aqueous bromfenac levels after repeat instillation with no cumulative drug effect; minimum aqueous concentration always remained above IC_{50}

Comparative Evaluation of Postoperative Pain Score, Summed Ocular Inflammation Score and Anterior Chamber Flare in Patients Undergoing Phacoemulsification in Phase II

Parameter	Group I (Control) Mean ± SD (n=15)	Group II (Once daily) Mean ± SD (n=14)	Group III (Twice daily) Mean ± SD (n=16)	P value
Pain Score				
Day 1	5.13 ± 1.06	2.21 ± 0.89	2.75 ± 1.18	<0.001
Day 7	2.73 ± 1.16	0.28 ± 0.61	0.81 ± 0.98	<0.001
1 month	0.6 ± 0.82	0	0	<0.01
3 months	0	0	0	-
Summed Ocular Inflammation Score				
Day 1	3.46 ± 0.91	1.25 ± 0.77	1.15 ± 0.76	<0.0001
Day 7	2 ± 0.32	0.35 ± 0.23	0.40 ± 0.20	<0.0001
1 month	0.76 ± 0.65	0	0	<0.0001
3 months	0.03 ± 0.12	0	0	0.64
AC Flare (photon count per millisecond)				
Day 1	11.4 ± 2.97	5.39 ± 1.54	6.02 ± 1.72	<0.001
Day 7	8.45 ± 1.79	2.74 ± 0.89	3.55 ± 0.88	<0.001
1 month	6.3 ± 1.77	1.65 ± 0.78	2.33 ± 0.77	<0.001
3 months	3.26 ± 0.79	0.90 ± 0.56	1.42 ± 0.68	<0.001

Clinical Efficacy

Ocular Inflammation & Pain

- **Mean pain score** significantly **higher in the control** group ($p<0.001$) as compared with OD and BD groups on POD1, with a gradual decrease in the postoperative pain over one month
- The **mean SOIS and AC flare** in both OD and BD groups was **significantly less than the control** group at all follow up visits.
- The patients in the OD and BD groups showed a rapid decrease in the anterior chamber inflammation with negligible inflammation at postoperative 1 month.
- There was **no significant difference** in the pain score, SOIS and AC flare between the **OD and BD groups** at any time point ($p>0.05$)

Comparative Evaluation of CDVA, IOP, CMT and Macular Volume in Patients Undergoing Phacoemulsification in Phase II

Parameter	Group I (Control) Mean ± SD (n=15)	Group II (Once daily) Mean ± SD (n=14)	Group III (Twice daily) Mean ± SD (n=16)	P value
CDVA (logMAR)				
Day 1	0.11 ± 0.10	0.08 ± 0.10	0.10 ± 0.09	0.67
Day 7	0.09 ± 0.08	0.07 ± 0.08	0.09 ± 0.08	0.8
1 month	0.09 ± 0.08	0.07 ± 0.08	0.09 ± 0.08	0.8
3 months	0.07 ± 0.08	0.07 ± 0.08	0.09 ± 0.08	0.8
IOP (mm Hg)				
Day 1	15.8 ± 3.38	16.6 ± 5.27	17.25 ± 2.86	0.59
Day 7	15.86 ± 2.16	15.57 ± 3.73	15.81 ± 2.37	0.95
1 month	15.13 ± 1.99	15.85 ± 2.79	15.62 ± 2.15	0.69
3 months	14.53 ± 1.80	15.42 ± 2.37	15.18 ± 2.22	0.5
CMT (µm)				
Day 1	227.46 ± 25.78	247.5 ± 25.38	243.31 ± 21.68	0.07
Day 7	240.8 ± 26.79	251.35 ± 28.87	251.25 ± 18.35	0.41
1 month	237.93 ± 27.70	235.35 ± 25.79	242.93 ± 22.83	0.7
3 months	219.86 ± 25.57	227.57 ± 28.38	232 ± 23.58	0.42
Total MV (μm^3)				
Day 1	9.72 ± 0.31	9.77 ± 0.57	9.73 ± 0.37	0.94
Day 7	9.84 ± 0.29	9.76 ± 0.59	9.8 ± 0.39	0.88
1 month	9.80 ± 0.26	9.5 ± 0.46	9.68 ± 0.44	0.13
3 months	9.57 ± 0.24	9.39 ± 0.47	9.58 ± 0.44	0.35

Clinical Efficacy

- CDVA, IOP, CMT and total macular volume were comparable between the three groups
- The efficacy of once daily or twice daily topical bromfenac 0.09% in reducing ocular pain and inflammation as compared with a placebo has been demonstrated in previous studies.[1-4]
- To our knowledge, this is the **first study comparing the clinical outcomes after once daily and twice daily** instillation of **bromfenac 0.09%.**

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4. *Donnenfeld ED, Holland EJ, Stewart RH, Gow JA, Grillone LR. Bromfenac Ophthalmic Solution 0.09% (Xibrom) for Postoperative Ocular Pain and Inflammation. Ophthalmology. 2007 Sep 1;114(9):1653-1662.e1.*

Conclusion

Pharmacokinetics

Achieving Therapeutic Aqueous Concentrations

- A **preoperative** instillation of **atleast two doses** of topical bromfenac 0.09% (either BD dosing for one day or OD dosing for two days) is required to achieve adequate therapeutic aqueous concentrations of the drug

Efficacy

Once Daily vs Twice Daily

❖**Both once-daily and twice daily** instillation of topical bromfenac 0.09% are **equally efficacious in reducing postoperative inflammation and pain** and are useful adjuncts to the conventional postoperative therapeutic regimen after phacoemulsification

Long-Term Effects

Preventing CME

❖**Long term studies** with large sample size may be required to assess the preventive effect of bromfenac on **cystoid macular edema**

Thank You

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