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Short Communication

Study of ocular penetration of flurbiprofen in human aqueous humour

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Introduction

Flurbiprofen is 2-(2 fluro-4-biphenyl)propionic acid; it is a non-steroidal anti-inflammatory drug which has been shown to be a potent inhibitor of prostaglandin synthesis. Because it is a new drug, flurbiprofen needs to be evaluated in respect of its penetration into the aqueous humour of the eye.

Methods using high-performance liquid chromatography (HPLC) have been reported for similar compounds, such as ibuprofen [1, 2] and indoprofen [3]. A gas chromatographic procedure has been described for flurbiprofen [4]. Spinder *et al.* [5] have determined ibuprofen and flurbiprofen in dog serum by HPLC. The ocular metabolism of flurbiprofen has been examined by thin-layer chromatography, HPLC and radioactive measurements [6].

The present communication describes a study of the penetration of flurbiprofen into the human aqueous humour after oral and topical administration in the treatment of ocular inflammation during senile cataract surgery.

Experimental

Equipment

A gradient analytical HPLC unit (Gilson Medical Electronics, France) with a binary pump and a Holochrome UV–vis detector was used for the chromatographic analysis. A 250 × 4.6 mm i.d. column packed with 5-μm C-18 Partisil 5 ODS3 provided with a guard column was used in the analysis. The mobile phase was acetonitrile–0.05 M acetic acid (40:60, v/v) and the flow rate was 2 ml min^{-1}. The UV detector was set at 254 nm with a chart speed of 10 mm min^{-1}; 10-μl injections were made into the chromatograph.

Reagents

All reagents were of analytical grade and solvents were of Lichrosolve grade from E. Merck. A pharmaceutical grade of flurbiprofen (Fair Deal Corporation, India) was used as received.

Standard solutions

A standard stock solution containing 0.03% (w/v) flurbiprofen was prepared by dissolving equimolar quantities of flurbiprofen and sodium hydroxide in triple-distilled water. Further dilutions were made with the mobile phase.

Preparation of eye drops

A 0.03% (w/v) flurbiprofen solution is used for topical dosing in eye. Since flurbiprofen is insoluble in water, an attempt was made to prepare eye drops of the drug by dissolving the equimolar concentrations of flurbiprofen and sodium hydroxide in triple-distilled water. These drops are suitable for administration in the eye and are now used in the Ophthalmology Department of the New Teaching Hospital, Jodhpur, during senile cataract surgery.

Sample collection, its treatment and methodology

The study was conducted on 31 patients of Dr S.N. Medical College, New Teaching Hos-

pital, Jodhpur. The aqueous humour samples were collected transcorneally by the surgeon at the time of cataract surgery in clean, dried and autoclaved vials. The cases were grouped as follows:

(1) Group 1 consisted of six cases of uncomplicated senile cataract who were dosed orally with one tablet of flurbiprofen (Arflur 50 mg) three times on the day prior to surgery and once 1 h before the surgery.
(2) Group 2 consisted of 15 cases of senile cataract uncomplicated by any ocular disease. They were dosed topically with 50 μl of 0.03% flurbiprofen eye drops four times at half-hour intervals on the day of surgery. Aqueous humour was collected at 30 min, 1, 2, 4 and 8 h after ceasing drug administration and accordingly group 2 cases were sub-grouped as 2A, 2B, 2C, 2D and 2E, respectively.

To monitor flurbiprofen in the aqueous humour of the human eye, a simple and sensitive HPLC method [7] developed in the author's laboratory was used, wherein at 254 nm, flurbiprofen was detected at the retention time of 8.3 min. For a blank determination, chromatograms were recorded initially with plain aqueous humour, i.e. of the untreated eye. This revealed several interfering peaks which may be due to endogenous biological material in the aqueous humour. For removal of interference and also to isolate the drug from the aqueous humour, the following sample treatment was necessary.

To the sample of aqueous humour (0.08–0.2 ml) an equal volume of acetonitrile was added with the aid of a micro-syringe and the mixture was centrifuged at 3500 rpm for 20 min to remove precipitated material. The clear supernatant liquid was evaporated to dryness under a stream of pure nitrogen. The sample was then reconstituted with a minimum volume of methanol and stored under refrigeration for subsequent analysis by HPLC. Quantitation of drug in the samples was achieved by reference to a calibration graph derived from the analysis of standard solutions.

Results and Discussion

The linear regression equation for standard flurbiprofen solutions in the range 100–500 ng ml^{-1} was: $y = 1.00 \pm x - 7.1 \pm 4.9$ ($n = 5$; correlation coefficient = 0.9996).

Table 1
Peak-height and corresponding drug level in the orally dosed group 1 patients

Sample no.	Peak-height at 0.02 AUFS (mm)	Concentration of flurbiprofen (ng ml^{-1})	Mean concentration* (ng ml^{-1})
1	3.0	17.5	
2	3.5	20.0	
3	4.0	22.5	17.0
4	2.5	12.5	
5	2.5	12.5	
6	3.0	17.5	

*Mean of six determinations each in duplicate.

Table 2
Peak height and corresponding drug level in topically dosed group 2 patients

Sample no.	Peak-height at 0.05 AUFS (mm)	Concentration of flurbiprofen (ng ml^{-1})	Mean concentration* (ng ml^{-1})
A_1	12.5	156.26	
A_2	11.5	143.75	150.00
A_3	12.2	150.00	
B_1	16.0	200.00	
B_2	21.0	260.00	
B_3	17.0	212.50	224.16
C_1	27.0	332.50	
C_2	25.2	311.25	
C_3	23.5	290.00	311.25
D_1	11.0	137.5	
D_2	13.0	161.90	
D_3	12.0	150.0	149.8
E_1	6.0	75.00	
E_2	5.0	62.50	
E_3	5.5	68.75	68.75

*Mean of three determinations each in duplicate.

Results for the ocular penetration of flurbiprofen are shown in Tables 1 and 2.

Patients dosed topically showed drug levels in the aqueous humour of 68.75–311.25 ng ml^{-1}. Orally dosed patients showed 12.5–22.5 ng ml^{-1} of flurbiprofen in the aqueous humour. All the above drug levels in the aqueous humour are sufficient to inhibit prostaglandin synthesis during surgery. Maximum absorption of the drug was found to occur 2 h after the topical administration of one drop of 0.03% flurbiprofen eye drops four times at half-hourly intervals.

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