

# Variability in the content of Indian generic ciprofloxacin eye drops

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**Background/aims:** Under-potent generic antibiotics sold in developing world countries may be contributing to positive selection of resistance organisms and to unpredictability in clinical outcome, leading to a loss of confidence among physicians locally. The objective of this study was to determine whether reports of unpredictable outcome for generic ciprofloxacin antibiotic eye drops in India could be the result of inadequate concentration of preparations sold by pharmacies.

**Methods:** 130 ciprofloxacin eye drop samples sold by pharmacies were collected from seven locations in north, central, and south India; 30 were randomly selected for testing. All samples were assayed using validated methods of reverse phase chromatography and fluorescence detection at a international antibiotic reference laboratory in the United Kingdom. Results were compared with advertised concentrations within the context of internationally accepted variability ranges.

**Results:** In total, six out of the 30 samples tested had ciprofloxacin concentrations lower than the standard advisory ranges of plus or minus 5% of stated content for 3 mg/ml pharmaceutical preparations. The ciprofloxacin content of these eye drops ranged from –36.4% to –16.1% of the stated content (median –21.73%). 24 out of 30 samples were found to be over the standard advisory ranges of plus or minus 5%, at a median of +19.42% (interquartile range (IQR) +14.28 to +25.13). Intra-batch variability of two selected samples was wide at –22.83% to +33.93% (n=11) and –17.07% to +31.20% (n=12).

**Conclusions:** Approximately 20% of generic ciprofloxacin eye drops, purchased without prescription in India were under-potent. In a number of preparations the antibiotic content was sufficiently low as to have a potential impact on clinical outcome and possibly lead to the selection of resistant isolates in individual patients. More widespread studies are justified to identify the extent of under-potency of widely used generic antibiotic medications in developing countries.

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The rising worldwide problem of antibiotic drug resistance is often considered to be associated with poor treatment concordance.<sup>1</sup> In many parts of south Asia widespread resistance to commonly used and affordable antimicrobial agents has made the treatment of infections such as pneumonia, dysentery, typhoid, malaria, neonatal sepsis, urinary tract infections, and tuberculosis challenging in these resource limited environments.<sup>2,3</sup> In these countries, inexpensive "over the counter" generic antibiotics undoubtedly allow access to affordable treatment for some of the world's poorest people. Recently, the WHO has expressed concerns over the potential impact of antimicrobial resistance in these countries,<sup>4</sup> and it has been suggested that legislation to curtail over the counter availability is necessary, with unsupervised use contributing to resistance.<sup>5</sup>

In countries such as India, where a third of the population buys prescription drugs, including antibiotics, without prescription<sup>6</sup> there is anecdotal evidence from local ophthalmologists that such preparations may be of variable potency with the suggestion that imported drugs are more predictable than generics. In response to these concerns of local physicians, we have conducted a study of the concentrations of ciprofloxacin generic eye drops sold by pharmacists without prescription in a number of towns and cities in India.

## MATERIALS AND METHODS

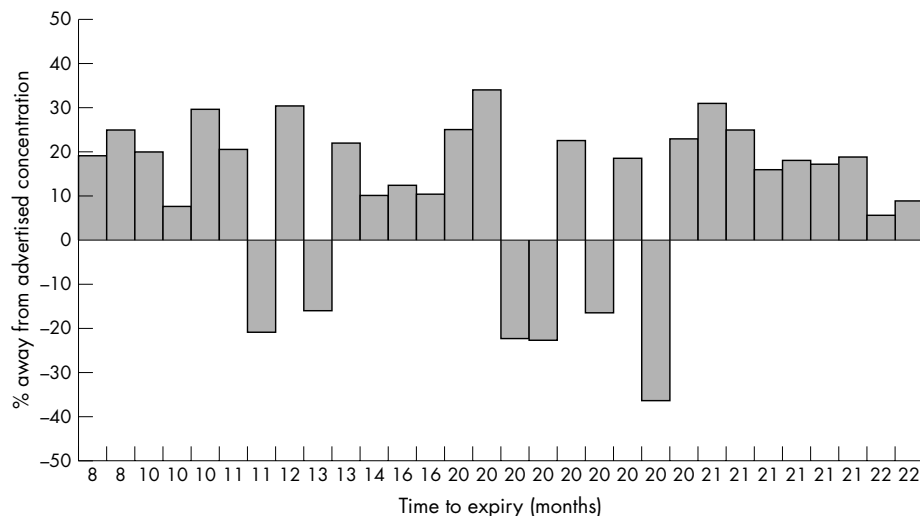
In all, 130 samples of ciprofloxacin antibiotic eye drops were collected from 20 pharmacies at seven locations along a route extending from Delhi in the north to Madurai in the south. This was an area totalling approximately 1 800 000 km<sup>2</sup> of India; the borders of this area being the three greatest distances between test locations. These pharmacies were

situated in Delhi, Lucknow, Kanpur, near Manjhanpur (District Allahabad, Uttar Pradesh), near Motickpur (District Barabanki, Uttar Pradesh), Madras (Chennai), and Madurai. The towns and cities had been chosen on the basis of a pre-planned non-research related route, and as many different manufacturers' products as possible were collected. Although this study design did not provide sampling from the whole of India, the populations of these areas in winter 2002–3 varied from many millions in the big cities to over 100 000 (Manjhanpur) and between 1000 and 10 000 (Motickpur)—representing a broad spectrum of urban and rural areas of India.

All 130 samples collected were divided into groups representing different manufacturers and batches. Thirty generic ciprofloxacin samples (3 mg/ml) produced as 10 batches from five different pharmaceutical companies were randomly selected for testing by block randomisation accounting for manufacturer and batch.

Subsequently, further examples were randomly selected from the two largest batches, which were below recommended concentration in initial testing. These were made by separate manufacturers of 0.3% ciprofloxacin eye drops and were used to estimate intra-batch concentration variation; total samples in each batch being 11 and 12 specimens respectively.

All 130 samples were within expiry dates and were stored at UK room temperature under dark conditions after being transported to London. The ciprofloxacin content was assayed for ciprofloxacin concentration under single masked conditions, at the Bristol Centre for Antimicrobial Research and Evaluation, along with samples of ciprofloxacin eye drops purchased in the United Kingdom.



**Figure 1** Ciprofloxacin generics in India (time to expiry in months for all samples is detailed on the x-axis).

The samples were assayed by a validated liquid chromatography method using reverse phase chromatography and fluorescence detection.<sup>7</sup> All samples were maintained at 4°C, in the dark, before assay. For assay, samples were warmed to room temperature, thoroughly mixed, and diluted 1:1000 before assay; there was no evidence of precipitation in any of the tested samples. Concentrations were calculated using the external standard method in reference to laboratory standard grade ciprofloxacin (Bayer PLC, Newbury, UK).

**RESULTS**

In total, six out of the 30 samples tested had ciprofloxacin concentrations lower than the standard advisory ranges of plus or minus 5% (2.85–3.15 mg/ml) of stated content for pharmaceutical preparations of 3 mg/ml (fig 1).

The ciprofloxacin content of these eye drops ranged from –36.4% to –16.1% of the stated content with a median of –21.73% (interquartile range (IQR) –22.83% to –16.43%).

A total of 24 out of 30 samples were found to have concentrations above the standard advisory ranges of plus or minus 5% with a median of +19.42% (IQR +14.28% to +25.13%).

The six under-potent samples were produced by three out of five pharmaceutical companies surveyed, were from three different batches, and were purchased from pharmacies separated by over 1000 km. Further samples were available from two of these companies and when subsequently assayed, ciprofloxacin concentrations in these ranged from 2.44–3.94 mg/ml (–19% to +31%) (n = 11) and 1.91–4.02 mg/ml (–36% to +34%) (n = 12). All of these 23 samples were outside the advisory range, confirming the earlier findings.

In general, aqueous solutions of ciprofloxacin are extremely stable and can be subjected to extremes of temperature without loss of potency, as demonstrated by the long shelf life of pharmaceutical preparations.<sup>7</sup> In contrast, aqueous solutions are susceptible to degradation by ultraviolet component of visible light. As all of the samples were purchased in cardboard boxes, and protected from light, this would suggest that our observations probably reflect quality assurance processes other than loss of potency on storage.

**DISCUSSION**

Ciprofloxacin’s bactericidal action results from interference with the enzyme DNA gyrase, which is needed for the synthesis of bacterial DNA. Topical ciprofloxacin readily penetrates the cornea and is absorbed by aqueous. Ocular

surface precipitation occurs in approximately 16% of treated patients as a result of pH changes with tear film contact. This often results in a change to management but is not thought to be associated with adverse corneal effect.

Although it is reassuring that in this study many samples had ciprofloxacin concentrations close to internationally recommended ranges it is of concern that a number of specimens tested had concentrations significantly outside the international recommended standard of plus or minus 5%. While it is uncertain if all six under-potent samples would produce differences in clinical response three of these were 22%, 23%, and 36% under-potent and it appears likely that these could directly influence clinical outcome.

Quality assurance aims at producing samples within international guidelines of plus or minus 5% of advertised concentrations. Over-concentration has increasing importance the more toxic an eye drop. Levels of over-concentrations of generic samples are difficult to interpret from a clinical standpoint, as ciprofloxacin precipitation seems well tolerated by the cornea for short periods. Nevertheless, concentration above 5% of the advertised concentration was seen in 24 of the 30 generic samples purchased from Indian pharmacies with a median concentration in these 24 samples of 19.4% (interquartile range (IQR) +14.28% to +25.13%). Furthermore, concentration levels greater than 20% of the advertised concentration were found in 11 out of 30 Indian generic samples.

Although our study design did not include the whole of India, it was such as to obtain a broad survey of the samples available in India under conditions similar to which the agents would have been used. We did not attempt to collect samples in a design reflecting either population distribution or volumes of medication used, as these data are not readily available. In collecting these samples, we simply attempted to obtain as wide a sample of available medications as possible, from a number of geographically distinct areas within the country. As such, there are limitations in applying the data obtained in the study to the overall situation in the country but, nevertheless, they provided a valuable insight to some of the problems that occur in the supply of generic ciprofloxacin eye drops in this population.

In conclusion, we have found that approximately 20% of generic ciprofloxacin eye drops, purchased without prescription in India were under-potent. In a number of preparations the antibiotic content was sufficiently low as to have a potential impact on clinical outcome and possibly lead to the selection of resistant isolates in individual patients.

Identifying the causes of under-concentration was not the aim of the study and proportions of free base, within samples, were not measured. The findings of this study suggest quality assurance processes, frequently, did not control concentrations of the generic ciprofloxacin eye drops to within satisfactory levels of variability. Our data would suggest that more widespread studies are justified to identify the extent of under-potency in these widely used generic medications.

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Approved by Moorfields Research Ethics Committee, reference: Weir1003.

The corresponding author accepts full responsibility that the data are genuine and the analysis conducted honest.

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## ECHO

### ROP claims sight needlessly



Please visit the British Journal of Ophthalmology website [www.bjophthalmol.com] for a link to the full text of this article.

**F**urther measures are needed to help avert the risk of lifelong blindness in preterm babies, the first population study of severe retinopathy of prematurity (ROP) has found. Fourteen preterm babies, out of 233 studied, developed lifelong blindness from severe ROP in one eye or both, some as a result of deficiencies in screening or treatment. The UK multicentre study also found that screening on the basis of gestational age and birth weight together, not singly, captured outliers in the study and potentially brought the screening criteria down to <29 weeks' gestational age and <1250 g birth weight, from current UK criteria of  $\leq 31$  weeks and  $\leq 1500$  g, respectively.

The review during 1997-9 found that national screening guidelines were followed in 72% of cases, but in 28% screening was too late or too infrequent. Also in 13 babies progression of the condition indicated that severity had been wrongly judged. In three cases in which follow up data were available non-compliance with screening guidelines led to adverse sight at one year. Treatment was delayed longer than recommended in five babies. In most babies ROP was bilateral (84%) and most severe with lowest gestational age and birth weight.

Babies with stage 3 ROP or worse were identified through the surveillance unit of the Royal College of Ophthalmologists, and data on clinical condition, screening and treatment, and outcome at one year were recorded by questionnaire.

ROP, a fairly rare disease confined to preterm babies, is largely, but not entirely, preventable by timely identification and treatment.

▲ Haines L, *et al*. *Archives of Disease in Childhood Fetal and Neonatal Edition* 2005;90:F240-F244.