

Correspondence

Widespread distribution of a single drug rifampicin formulation of inferior bioavailability in South Africa

I am writing to you with reference to a recent article published in the April 2002 issue of the *Journal*.¹

Following the release of this article, a misperception has been formed amongst some medical practitioners and lay press in India that batches of Lupin's rifampicin products were withdrawn from the South African market as a direct result of failing in bio studies. This is a wrong perception and I would like to take this opportunity to set out the facts surrounding this issue. Further, the title of the article suggests that only Lupin's formulation had inferior bioavailability. This, we submit, requires reconsideration in the context of the internationally accepted Rifampicin C_{max} cut-off at 8.0 µg/ml for bio considerations. (Even the referred article accepts and mentions this reference standard.)

The above-mentioned study (which was carried out purely for 'academic reasons', as we learn from Dr McIlleron) clearly highlights the need for undertaking bioavailability studies even with single ingredient rifampicin products. As is known, one also needs to keep in view the peculiarities and 'idiosyncrasies' of rifampicin as a drug. We too, therefore, firmly believe that bioavailability of rifampicin cannot be taken for granted and, guided by this belief, we regularly repeat bioavailability studies of our rifampicin-containing products at the WHO-certified National Institute of Pharmaceutical Education and Research (NIPER), Chandigarh, India.

May I draw your attention to the fact that the South African regulatory authorities did not ask us to withdraw our products (Rifacap 150, Rifacap 450) due to any sub-bioavailability, nor did they ever ask us for any bioavailability studies.

Therefore, it is important to appreciate why and when the products were actually withdrawn by Lupin.

We had made an application in January 1999 to the South African regulatory authority to allow us to continue to supply Rifampicin 150 and 450 mg capsules with minor change in excipients following a change of manufacturing location. After 6 months there was no response/objection raised by the regulatory authority; hence, we manufactured and supplied the product as intended.

Later, however, in January 2000 (one year after our application and 6 months after our supplying the products), the South African regulatory authority reverted to us in response to our year-old application, advising that we should withdraw the product as they

couldn't view a change of excipient as 'minor'. They also advised us to undertake new administrative formalities. This is why we withdrew the two products from the market, and the withdrawal process was completed within a few weeks. Needless to mention, the batches of the products referred to in the reported bio study are the same as above, and hence had no relevance to any in-market stocks after March 2000.

Unfortunately, the medical community and other readers are misinterpreting that we had been 'asked' to withdraw our products due to sub-bioavailability. This is evidently incorrect. In fact, the compilation, analysis, authoring and submission (15 June 2001) of the study took place more than 15 months after the total withdrawal of the Lupin products referred in the report. I need not highlight the fact that unfortunately India has the highest global burden of tuberculosis, and any such creation of avoidable confusion would seriously hamper our image and participation in helping TB eradication programmes, although the study has no relevance to any in-market stocks of Lupin's rifampicin products, today.

Therefore, through this communication we humbly request you to clarify the following to your readers through a suitable release in an edition of your *Journal*:

- The April 2002 IUATLD article on the Cape Town bio study appears to have created distorted perceptions amongst some sections of the medical fraternity and lay press, resulting in queries seeking explanations from our office.
- This is to state that the referred study was conducted purely for academic reasons and was not undertaken under the direction of any regulatory authority.
- The methodology adopted in this study has raised similar issues through findings on all the three brands tested in terms of the C_{max} cut-off at 8 µg/ml. Since 8 µg/ml is the right cut-off reference for C_{max} for rifampicin (as mentions the referred study), no exceptional(adverse) inference should be drawn upon any of the products tested.
- The study concludes that regulatory authorities must make periodic human bioavailability studies mandatory, particularly for rifampicin-based products.
- This is to put on record that the Lupin products (batches referred to in the article) were withdrawn in February–March 2000, i.e., well before (about 15 months) the completion, compilation and submission of the referred study in June 2001. While there was no deliberate intention to conduct a bio study on a commercial product that was already

withdrawn from the market for reasons unassociated with rifampicin bioavailability (and hence, ceased to continue to be an 'in-market' product for usage), it should be noted that the published study, its findings and withdrawal of the referred batches of Rifacap from the South African market are two separate subjects and are not inter-linked at all. We regret any confusion that may have occurred through correlation of these issues due to the published report.

- We would, therefore like to advise our readers not to correlate the research study as completed in June 2001, with the withdrawal of any product that had independently happened in March 2000 for unassociated reasons.

A clarification from your office on the above subject will go a long way in establishing the actual importance of the above mentioned study published in your prestigious journal, while also removing the misunderstanding caused on the subject of withdrawal of our products from South African markets, and also about the adverse inference on only one of the three products tried for the prescribed bioavailability norms (8 µg/ml cut-off for C_{max}).

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Reference

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In reply

Our purpose in reporting the finding of inferior bioavailability was to highlight the responsibility of manufacturers and regulatory authorities in ensuring that the products distributed to patients should be of high quality and adequate bioavailability. In this case, the manufacturers failed to submit bioavailability data compliant with the regulatory requirement. The article made that clear.

Bioavailability testing for rifampicin-containing products, both single drugs and fixed dose combinations, is mandatory. This should be done by bioequivalence testing in line with internationally accepted guidelines. The accepted lower limit of the recommended range of rifampicin concentration is 8 mg/l, based largely on studies of healthy volunteers. Patients, once established on therapy, will in all probability have lower levels due to rifampicin's autoinduction and other factors. This does not excuse the use of preparations of inferior bioavailability.

The mean maximal concentration of the Lupin

batches in question was reduced, compared with that of the other formulations that were tested. Of greatest concern was the number of patients taking these batches who had peak rifampicin levels below 4 mg/l: 56.6% with the Lupin products, compared with 21.5% for the other formulations. The relevance of the article, even though the specific batches have been withdrawn, is to highlight the need for study of bioavailability in tuberculosis patients for both single drug formulations and fixed dose combinations.

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Phage tests for diagnosis and drug susceptibility testing

In response to the recent Editorial by Takiff and Heifets,¹ I would like to clarify that the development of the method described by McNerney et al.² for rapid screening for resistance to rifampicin was funded by the Department of International Development, UK (DFID), and was not undertaken in collaboration with the manufacturers of the FASTPlaque kits. One of the benefits of the method we describe is that 'in-house' maintenance of phage stocks reduces costs by alleviating the need to purchase commercial kits. The microwell plate method we describe was developed to provide rapid, low cost screening of isolates for MDR-TB. It is simple to perform, and permits rapid screening of large numbers of isolates. In contrast to the other phage-based and phenotypic methods it does not require quantification of the inoculum, thus reducing the labour requirement. We have not yet demonstrated sufficient accuracy for determination of susceptibility to isoniazid or ethambutol with this format of the test and do not currently recommend the method for monitoring individual patients. We concur with the authors that alternative methods may permit more rapid identification of MDR-TB by direct testing of clinical specimens. Indeed, in our publication we reported the use of molecular tests to detect rifampicin resistance from the sputum of smear-negative patients.

Regarding the specificity of phage tests, with the notable exception of *M. avium*, mycobacteriophage D29 successfully replicates in a wide range of mycobacteria, including pathogenic and environmental strains. Riska and colleagues previously reported a confirmatory phage test for *M. tuberculosis* complex bacteria utilising NAP (p-nitro-alpha-acetylaminobeta-hydroxy propiophenone).³ We have investigated use of a low cost alternative, ρ nitrobenzoic acid, to

inhibit non-tuberculosis bacteria in the microwell phage assay. However, despite encouraging preliminary results we feel this test is not sufficiently robust for application in the routine diagnostic laboratory.

We have also been investigating the use of phages for the diagnosis of pulmonary tuberculosis from sputum. In collaboration with the Chest Diseases Laboratory and University Teaching Hospital in Lusaka, we have tested a low cost 'in house' method and the commercial *FASTPlaque* kit. In common with the laboratory in Pakistan, contamination problems were observed when using the commercial kit protocol, suggesting that this kit may not be appropriate for tropical settings or where delays are experienced in transport of specimens to the reference laboratory. Analysis of the data from these studies is being undertaken prior to publication of findings.

In conclusion, we would like to point out, as is so often the case with tuberculosis, that this work is not entirely novel. Researchers at the Institute Pasteur in Paris used D29 phages to detect *M. tuberculosis* and drug resistance twenty years ago.⁴ However, their preferred method of phage inactivation was to use sulphuric acid rather than the ferrous compounds we use today.⁵ Their ultimate goal was investigation of *M. leprae* using phages, a goal which, sadly, has yet to be realized.

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In reply

The letter by Ruth McNerney in response to our Editorial¹ is another addition to the discussion about the value of the phage-related procedures such as the *FASTPlaque* technology.² According to this letter, the report by McNerney and her colleagues³ described an 'in-house' procedure, which is, in the authors' opin-

ion, more cost-effective than the commercially available kit for the *FASTPlaque* technology and may have some other advantages.

While the preference between these two approaches in regard to their accuracy and reliability would require a comparison study in one setting, the question of cost could have been addressed by a comprehensive calculation that would include the cost of supplies, labor and overheads. Unfortunately, such a calculation has been presented neither by this group nor by those endorsing the commercially available kit. It is reasonable to anticipate that the cost and other advantages and disadvantages of both procedures can be different in different countries, especially outside of the UK.

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Use of the *FASTPlaque* test for TB diagnosis in low-income countries

We welcome the recent editorial by Drs. Takiff and Heifets on the use of the *FASTPlaque* TB test for the rapid diagnosis and susceptibility testing of tuberculosis (TB) in low-income countries.¹ We agree that the key finding was that one-half to two-thirds of smear-negative culture-positive specimens were detected by *FASTPlaque* TB with high specificity.^{2,3}

We would like to highlight several comments in the editorial. The authors noted that the phage could be amplified by almost any mycobacteria. Whilst the phage is theoretically capable of cross-reactivity with certain strains of non-tuberculous mycobacteria (NTMs), in practice the test has high selectivity for *Mycobacterium tuberculosis* complex. A Spanish study in which 32% (30/95) of mycobacterial isolates were NTMs reported 98.5% specificity for *M. tuberculosis*.⁴ In addition, it is recognised that the prevalence of NTMs is generally low in high TB incidence countries. This is supported by the high specificity of smear microscopy in such settings.

The authors correctly commented on the challenge of contamination in developing country settings. Much of the contamination experienced was on culture rather than the *FASTPlaque*TB test, possibly as a result of the longer incubation period of culture. Contamination has been largely resolved by the provision of antimicrobials by the manufacturer of the *FASTPlaque*TB test.

The *FASTPlaque*TB test gave a false-negative result in approximately 13% of smear-positive culture-positive specimens. This is somewhat unexpected, given that much lower numbers of AFB are detected in smear-negative specimens. There are several possible explanations for this apparently paradoxical observation. The decontamination may affect the expression of phage receptors and *M. tuberculosis* viability. In addition, inhibitory components are present in sputum in varying amounts (unpublished data). Currently, the *FASTPlaque*TB test is not intended to replace smear microscopy; it is recommended to be used in conjunction with smear microscopy to detect a significant fraction of smear-negative TB patients.

The figures quoted in the editorial for the false positivity rate were misleading. Of all the specimens tested that were smear-negative culture-negative, only 1.6% (4/252)³ and 0.5% (7/1369)² gave false-positive results. The impact of such false-positive results on the usefulness of the test in the diagnosis of smear-negative TB has, in our opinion, been overstated. Whereas no laboratory test can be entirely conclusive in isolation, we believe that the *FASTPlaque*TB test's specificity and sensitivity make it a useful aid to TB diagnosis.

We welcome the authors' comments on the value of a rapid rifampicin resistance test. As alluded to in the editorial, many countries rely on solid culture for mycobacterial isolation. The *FASTPlaque*TB-RIF test can be performed directly from solid culture, as reported in an earlier article,⁵ resulting in significant time and money savings as the authors propose.

We concur with the suggestions as to how *FASTPlaque*TB could be incorporated into laboratories. *FASTPlaque*TB could be used in the diagnosis of patients with clinical suspicion of TB but negative sputum smears, while *FASTPlaque*TB-RIF could act as a rapid screen for MDR-TB from conventional culture, allowing those patients requiring alternative treatment to be rapidly identified.

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In reply

We would like to reaffirm our previous statement that we consider the *FASTPlaque* test a useful addition in some laboratories as a tool enhancing the probability of a provisional diagnosis of TB by AFB smear examination, since this test was positive in one-half to two-thirds of smear-negative sputum specimens.¹ The authors of the letter agree with our assessment that 13% of false-negative results of the *FASTPlaque* test (among smear-positive culture-positive specimens) is a serious problem. On the other hand, we agree with the authors that the issue of false-positive results must be clarified. They are correct that the rate of such results was very low, if calculated as a ratio to a large number of all smear-negative specimens. At the same time, there is concern with regard to the positive *FASTPlaque* test results in smear-negative patients, who represent the primary target of this test.² Culture was negative in five of 26 patients of this group (19%), which would require final confirmation or rejection of TB diagnosis in these patients by thorough clinical and radiological examination.

Only with clear understanding of these limitations can the *FASTPlaque* test be useful, in combination with the AFB smear examination, as an additional tool for the provisional diagnosis of TB.

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Superficial fungal infection of the skin during treatment of tuberculosis

A 62-year-old male presented to our hospital in 1994 for treatment of sputum culture-positive pulmonary tuberculosis. The causative bacilli were subsequently found to be isoniazid-resistant. He was treated with standard short-course drugs, including streptomycin, isoniazid, rifampicin, ethambutol and pyrazinamide during the initial 5 months. Due to gastrointestinal intolerance to pyrazinamide and visual toxicity due to ethambutol, the continuation phase of treatment included ofloxacin 400 mg once daily and rifampicin 450 mg once daily for 8 months. He was deemed to be cured and treatment was stopped in October 1995.

During follow-up in 1999, he experienced an episode of clinically diagnosed tinea corporis and was treated with oral and topical antifungal agents for several months by the dermatologist. In May 2001, he was found to have recurrent pulmonary tuberculosis in the left upper lobe as well as tuberculous spondylitis in the lower thoracic spine. Treatment was begun with daily rifampicin (450 mg), ofloxacin (500 mg) and pyrazinamide (1.25 g), and twice-weekly administration of streptomycin (0.6 g).

After 6 months of such treatment, his clinical condition had improved significantly in terms of body weight gain and subsidence of spinal pain. However, he also noticed a somewhat itchy fulminant erythematous rash, progressively developing all over the trunk and limbs, over the preceding few weeks. Blood tests revealed hyper- γ -globulinaemia and eosinophilia. He was initially suspected to be suffering from a drug hypersensitivity cutaneous reaction. Cessation of all anti-tuberculosis drugs in December 2001 and application of topical steroids resulted in a worsening of the dermatitis. A cutaneous biopsy revealed dermatophytosis in January 2002. He was then treated with terbinafine systemically and tioconazole topically,

with clinical improvement and subsidence of eosinophilia. Assessment of his blood lymphocyte subsets and functions revealed no abnormality; HIV serology was negative. Subsequent treatment with rifampicin and pyrazinamide since February 2002 has not resulted in a recurrence of his skin problem.

Although streptomycin and rifampicin have relatively broad antimicrobial activities, they have not been reported in association with fungal superinfection. However, fungemia and other fungal infections have been definitely reported in immunocompromised patients receiving fluoroquinolones for prophylaxis.^{1,2} Apart from candidal thrush, fungal infections, during long-term fluoroquinolone administration have not been previously described.^{3,4} This brief case report should alert clinicians to superficial fungal infection of the skin that might be related to ofloxacin therapy. It is important to distinguish such a fungal dermatitis from a more common entity, drug-induced hypersensitivity reaction, lest this lead to an unwarranted cessation of anti-tuberculosis drugs in patients requiring such therapy.

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