Reply

I have suggested that treating typhoid fever patients with furazolidone as a single agent is best avoided(l) based on the fact that this drug achieves negligible serum levels(2,3) and poor bactericidal levels in blood(4). This may have medicolegal implications as the legal expert will try to find out whether the treatment given is appropriate. In this regard the consultant may have to explain the rationale of treating a systemic infection with a drug known to achieve negligible serum levels. The second query is whether furazolidone is an accepted treatment modality in typhoid fever. It is worth noting that furazolidone is not mentioned as a treatment modality in text books of international repute. Non standard treatment has a standing only when it is undertaken with the approval of the ethical committee of the hospital which is the rule in a study protocol.

The letter hints at the inappropriateness of my using furazolidone even after my suggestion against its use. Please note that my observations regarding the use of furazolidone had come after the studies quoted(4,5) had been completed. Since the communication referred to(1) was in response to a letter, it preceded the publication of the results of one part of our study(5). Hence it seemed as though I have been using furazolidone even after my own suggestion against it's use. It may also be noted that furazolidone was being used under an approved study protocol.

There is no standard recommended dose of furazolidone for typhoid fever. On review of studies of last 30 years I find various dose regimens ranging from 7.5 to 20 mg/kg/day. Since most authors used a dose of 7.5 mg/kg/day, we opted for a higher dose hoping for a better response. Regarding the use of furazolidone in multidrug resistant typhoid fever, an editorial(6) had suggested a dose of 20 mg/kg/day *along* with another drug (co-trimoxazole).

Dutta *et al.(7)* studied children with both blood and stool cultures yielding Salmonella typhi, having no other problems except for diarrhea and with a dramatically rapid response to treatment. One may argue that these point towards an immunocompetent host though a study of cell mediated immunity (CMI) could have resolved the issue better. Assuming that the CMI was good enough to tackle the systemic bacterial load, the bactericidal effects of furazolidone in intestine may have depleted the organisms available in the intestine for continued re-entry into the system and thus the clinical response may be explained(4). In studies of CMI by leukocyte migration inhibition tests it was demonstrated that complicated and potentially fatal infections occur in patients with weak or absent CMI(8).

An initial clinical response within 24-48 hours and complete defervescence in 3.1 days with a low dose ciprofloxacin therapy demonstrated by Dutta *et al.(7)* is a surprisingly rapid response compared with our experience of multi drug resistant typhoid fever cases.

There is no denying of the fact that based on the inclusion and response criteria used in studies, varying proportion of patients have recovered with furazolidone treatment. But that alone does not justify its use if it does not stand scientific reasoning. The fatality rate of adults with typhoid fever in the preantibiotic era was around 12% and only 10% of the recovered patients had relapses(9)-meaning that the majority had recovered without any antibiotics. It stands

to reason to believe that this spontaneous recovery can be hastened even by an inappropriate drug like furazolidone Whether to use furazolidone or not in properly selected patients is for the individual consultant to decide but it should be based on scientific reasoning.

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Reply

It is an established fact that if the infected strains of *S. typhi* are not multi-drug resistant, chloramphenicol, trimethoprim-sulphamethoxazole or ampicillin are the recommended drugs for typhoid fever. However, resistance of *S. typhi* strains to these drugs is approaching an unacceptably high level world wide(l,2). Currently, multi-drug resistant *S. typhi* are being encountered with increasing frequency in India(3-6) and the treatment of typhoid fever particularly in children has become a therapeutic challenge. Emergence of multi-drug resistant strains of *S. typhi* has also necessitated use of ciprofloxacin to treat typhoid fever in children(7) despite controversy over its use in individuals in this age group(8). Few studies showed the usefulness of third generation cephalosporin(9,10) but these drugs are expensive and are available only for parenteral administration.

In contrast, *in vitro* studies of *S. typhi* strains isolated in Calcutta and elsewhere show that the isolates are susceptible to furazolidone(3,6,ll). Several clinical alternative to chloramphenicol in the treatment of typhoid fever(12,13) even if it is caused by multi-drug resistant strains of S.