

# FURAZOLIDONE IN TYPHOIDFEVER— CORRELATION OF CLINICAL EFFICACY WITH SERUM BACTERICIDAL ACTIVITY

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## ABSTRACT

*Treatment of typhoid fever with furazolidone produces a high cure rate. This is a clinical curiosity, as furazolidone is described to be poorly absorbed. The present study examined whether furazolidone could produce unequivocal clinical response and, if so whether this was due to the drug producing bactericidal levels in the serum. Twenty one patients selected by defined criteria were treated with furazolidone and evaluated for definite clinical response in 5-7 days. Bactericidal activity of pre, dose and post dose sera were estimated in seven patients showing definite clinical response. All the seven patients had a clinical cure without the drug producing significant bactericidal levels in the blood. Hence we concluded that the major site of action of furazolidone was in the intestine. It is our postulate that the organisms reaching the intestine in large numbers from bile are prevented from gaining re-entry into the circulation by the action of furazolidone in the intestine. After repeated cycles of entry of organisms into the intestine from bile and the simultaneous prevention of its re-entry into the circulation, the number of organisms remaining in circulation comes down considerably, thus helping the immune system to bring about a cure.*

**Keywords:** *Furazolidone, Typhoid, Blood bactericidal activity, Absorption.*

Clinical efficacy of furazolidone in typhoid fever has been reported by many authors from different parts of India both in adults and children. A review of\* literature reveals that furazolidone achieves negligible serum levels after oral administration. The reported serum level of the drug is in the range of 1.5 µg/ml or less(1) while the minimum inhibitory concentration of furazolidone for *Salmonella typhi* is 2-5 µg/ml(2). A controversy has been on for quite some time with some authors suggesting that furazolidone should not be used in typhoid fever because of its poor serum levels while others favor its use because of good clinical response. The present study was aimed at looking into this controversy. The study was designed to find out whether patients with typhoid fever could respond unequivocally to furazolidone and if so whether this response was due to the drug producing bactericidal effect at these serum levels.

## Material and Methods

All patients admitted to the Pediatric Wards of Medical College, Thiruvananthapuram in the year 1992 with clinical diagnosis of typhoid fever by standard criteria were started on oral furazolidone 15 mg/kg/day in four divided doses immediately after drawing

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blood for clot culture. We then excluded all patients whose clot culture failed to yield *Salmonella typhi* sensitive to furazolidone (by Stokes diffusion method using standard *Escherichia coli*, NCTC 10418 as control to avoid technical error)(3,4)- Also excluded were patients whose blood culture yielded organisms sensitive to any of the antibiotics the child was receiving from local hospitals. This was done to avoid the previous treatment interfering with the assessment of furazolidone as a single agent producing the clinical response. For the purpose of our study we accepted patients as having responded to furazolidone only if they were afebrile within 5 days or had substantial reduction of temperature within 5 days and went on to become afebrile within 7 days. Since we started treatment immediately following withdrawal of blood for culture, our criteria for response meant that those who had responded did so within 5-7 days of having yielded a positive clot culture. This quick response cannot be a "natural cure" described in pre-antibiotic era where the disease pursues a prolonged course with a slow resolution of signs and symptoms and the fever decreases slowly by "lysis"(5). Hence, it should be considered that the drug was effective in patients responding to our treatment protocol. Those who responded were continued on furazolidone for a total period of 14 days. They were followed up for two weeks after the completion of treatment for evidence of clinical relapse. Those who had clinical evidence of relapse had their blood culture repeated to confirm this.

Serum bactericidal assays were done

after the patient had been on furazolidone for at least 48 hours. Two serum samples were taken—one just prior to the next dose of furazolidone ("pre-dose") and the other  $VA$  hours after a dose of furazolidone ("post-dose"). Doubling dilutions of the sera were incubated over night at 37°C with the broth culture of *Salmonella typhi* isolated from the very same patient. The tube with the greatest dilution showing no turbidity (no growth) was taken as the bactericidal level (expressed as bactericidal up to that particular dilution). Contents from this tube were sub-cultured to ensure maximum inhibition.

Undiluted serum was not subjected to the testing for bactericidal activity since even without any drugs serum has the ability to inhibit the growth of enteric organisms(6,7). It is to get rid of this inhibitory effect of serum that clot culture is done in preference to Wood culture in typhoid fever.

In the estimation of serum bactericidal activity the inhibition of growth of *Salmonella typhi* obtained is the combined effect of the drug and the body's immune mechanisms like antibody, complement, *etc.* Since immunological factors are available both in the pre dose and the post dose sera, any enhanced bactericidal action of post dose serum must be due to the drug. This is the basis of selecting serum bactericidal assay as the method for assessing the drug effect *in vivo*.

As per our criteria for patient selection, we excluded patients who had been on antibiotics from local hospitals, to which the organisms isolated subsequently were shown to be sensitive.

Because of this exclusion criteria all patients who were selected for trial with furazolidone turned out to have multidrug resistant typhoid fever (MDRTF). MDRTF patients not responding to furazolidone were individualized to receive treatment with various drugs singly or in combination depending on sensitivity and cost of therapy but with emphasis on avoiding potentially toxic drugs like ciprofloxacin. Hence, we did not have a group of children with MDRTF uniformly receiving the same drug for comparison with the data on furazolidone. However, to avoid methodological errors and to have an idea of the bactericidal levels achieved by an established therapeutically effective drug, we performed bactericidal assay of pre dose and post dose sera of adult patients with MDRTF responding to oral ciprofloxacin 500 mg twice daily. The patient selection and the criteria for response were the same for our study group and the group of adult patients.

## Results

The study group consisted of 21 patients with clot culture yielding *Salmonella typhi* sensitive to furazolidone but resistant to chloramphenicol, ampicillin and cotrimoxazole (MDRTF). The average duration of fever on admission varied from 9 days to 20 days. All the 21 patients were treated with furazolidone and they tolerated it very well without significant vomiting. On 2 occasions when the patient vomited within 1 hour of ingestion of furazolidone, the dose was repeated. None required antiemetic therapy.

Of the 21 patients 7 (33%) became afebrile within 7 days (3 within 5 days and 4 within 7 days) and remained relapse free. Estimation of bactericidal levels were done in these 7 patients using pre dose and post dose sera. The results showed that after furazolidone, the serum was not bactericidal at more than 1/2 dilution (*Table I*). It also showed the lack of significant difference of bactericidal levels between the pre dose and the post dose sera.

No meaningful correlation could be established between the duration of fever on admission and the response to treatment. Patients who did not respond to furazolidone therapy were put on alternative regimens and all of them made uneventful recovery.

A group, of nine adult patients with MDRTF becoming afebrile within 5-7 days of treatment with ciprofloxacin were selected for comparison. Serum bactericidal levels of post dose serum was significantly higher than that of pre dose serum in these patients (*Table II*). Serum was bactericidal upto 1/64 dilutions in 7 out of 9 patients.

**TABLE I** -*Assay of Bactericidal Activity of Serial Dilutions of Pre dose and Post dose Sera of Seven Patients Responding to Furazolidone Therapy*

Serum bactericidal levels -----		No. of patients (n=7)
Pre dose	Post dose	
Not bactericidal at 1/2 dilution	Not bactericidal at 1/2 dilution	5
Not bactericidal at 1/2 dilution	Bactericidal at 1/2 dilution	2

**TABLE II-** Assay of Serial Dilutions of Pre dose and Post dose Sera of Nine Adult Patients with MDRTF Responding to Oral Ciprpfloxacin

Serum bactericidal levels		No. of patients (n=9)
Pre dose	Post dose	
1/8 dilution	1/32 dilution	2
1/16 dilution	1/64 dilution	7

### Discussion

Since all patients had organisms sensitive to furazolidone *in vitro*, an enhanced bactericidal activity after a dose of furazolidone was expected in those who responded. Instead our study showed that the serum bactericidal activity after a dose of furazolidone did not differ appreciably from that before the dose (even though we had used a higher dose than is used generally)(8-11). This confirms that furazolidone achieves poor blood levels. The metabolites of furazolidone that are absorbed are not bactericidal. Hence for clinical purposes, furazolidone is a non-absorbable drug.

Serum should be bactericidal at V4 to 1/8 dilutions or more to have good correlation with clinical response(3,12). Thus the bactericidal action demonstrated at 1/2 dilution in 2 cases on furazolidone is below the generally accepted levels for clinical response. This becomes very obvious when we compare this with the result of adult patients treated with ciprofloxacin where serum even after 1/64 dilution was still bactericidal. Hence, we conclude that furazolidone does not achieve signifi-

cant bactericidal levels in the serum. This is consistent with the literature showing insignificant serum levels after oral furazolidone(2). In spite of this, and even after using rigid criteria for response, we could demonstrate unequivocal response without relapse in 33% of our MDRTF patients. Many authors using furazolidone have reported a therapeutic success in excess of 80%(8,10,11) using more liberal criteria for patient selection and response. Hence we assume that furazolidone brings about a cure in typhoid fever by its action locally in the intestine.

That furazolidone has a good local action in the intestinal tract, is shown by the excellent response obtained in giardiasis and various bacterial diarrheas like *E. coli*, *Shigella*, *Cholera*, etc.(13). *Escherichia coli*, *Klebsiella* and *Staphylococci* -hive *in vitro* sensitivity to furazolidone(2) but when used to treat systemic infections due to these organisms, furazolidone is ineffective. This is in concordance with our results showing an insignificant bactericidal activity in the blood.

It was suggested that during secondary bacteremia in typhoid fever, the main traffic of organisms is from blood to intestinal tract(7). This is supported by the fact that from the second week onwards, blood culture becomes increasingly negative while stool culture is more often positive. It seems that typhoid bacilli preferentially come out into the intestine in large numbers to overcome the inhibitory effect of normal flora thus enabling it to be passed out in stool and infect others. Thus the intestinal tract appears to be a major area of traffic of typhoid bacilli from where part

of if: re enters the circulation. In our opinion this entero-systemic re-entry is the major route of supply of organisms into the circulation. Cultures taken at autopsy give almost pure cultures of *Salmonella typhi* in the upper intestine while lower down bacilli becomes less numerous(7). This at least partly must be due to the entero-systemic re-entry.

Reviewing the literature on the use of furazolidone in typhoid fever, we have found that the majority of the patients in these studies were Widal positive but culture negative cases<sup>^</sup>, 10,11). We believe that culture negative patients continue to be febrile because of the entero-systemic re-entry of the organisms. Hence when a drug like furazolidone which acts in the intestinal tract blocks this entero systemic re-entry, the supply of organisms to the circulation is cut off and the patient responds. When the blood culture is negative, the number of organisms, remaining in circulation must be small enough for the body's immune mechanisms to tackle. This may be the reason for the excellent response reported by these authors.

Our study and some other published studies(9) have shown that there are a proportion of cases which are blood culture positive and still respond to furazolidone. Possibly the organisms go on entering the intestine in plenty but their re-entry back into the circulation is prevented by furazolidone. After a few *Y* such cycles the system is depleted of organisms, thus helping the immune mechanisms (especially the cell mediated immunity) to bring about a cure. However, since we have established

that furazolidone has got no significant action in the blood, we consider it unwise to use it as a single drug in the treatment of cases with positive blood cultures.

The fact that furazolidone tackles *Salmonella typhi* effectively in the intestine and that a proportion of patients have been cured by this local action alone raises an interesting possibility of combining this drug along with a systemically active drug in the treatment of typhoid fever. Whether this can have an additional benefit as compared to monotherapy with a systemically active drug needs to be looked into.

Our study has identified the intestinal tract as an important site to tackle the organisms as far as the treatment of typhoid fever is concerned. So whether a drug administered orally has advantage over, its parenteral use is another area of interest. In situations where oral preparations are not generally available as in the case of third generation cephalosporins, there is a theoretical advantage of using drugs like cefoperazone or ceftriaxone which achieve higher concentrations in the intestine due to their excretion in bile. Reports have already appeared showing that cefoperazone produces significantly better clinical response as compared to cefotaxime(5).

In conclusion we arrive at the postulate that the blocking of entero systemic re-entry is the main mechanism of action of furazolidone in typhoid fever. Although furazolidone does not produce bactericidal levels in the blood it can cure a proportion of patients with typhoid fever by its local action in the intestine. This can explain most of the

controversies existing in the field of treatment of typhoid fever with furazolidone.

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