of pharmacogenomics in clinical trials. Most of the trials employing pharmacogenomics were on cancer and psychiatry. Blood sample for pharmacogenetic study was usually collected at baseline visit in most of the studies.

Informed consent forms contained sufficient information in all the studies. But none of the consent forms mentioned about the fate of the sample collected once the study is complete. This needs to be clearly mentioned in the consent document. Consent for pharmacogenetic part of the study seems to be freely given, once the subject enrolled in the main study protocol, as there are no direct risks involved. All the patients who took part in the main study participated in the pharmacogenetic part of the study also. It is the responsibility of the investigator to see that the patient has given consent after sufficiently understanding the importance of giving blood sample for pharmacogenetic study.

Pre-screening clinical trial subjects by pharmacogenomics should allow the clinical trials to be smaller, faster and therefore less expensive; therefore, the consumer could benefit in terms of reduced drug costs. Finally, the ability to assess an individual’s reaction to a drug before it is prescribed will increase a physician’s confidence in prescribing the drug and the patient’s confidence in taking the drug, which in turn should encourage the development of new drugs tested in a like manner.\(^1,2\) Another potential use of pharmacogenetics is that a drug that has not been shown to be adequately safe and effective in a clinical trial on an entire population may achieve that goal in a genetically defined subset of the population.\(^3\) A recent analysis of adverse drug reactions (ADRs) showed that 59% of drugs causing ADRs are metabolized by polymorphic enzymes as compared to 7-22% of randomly selected drugs.\(^4\) This suggests that dose based on individual metabolizing genotype may reduce the risk of ADRs of certain drugs. Similarly, if a breast cancer patient has a tumor that is HER-2 (human epidermal growth factor receptor 2) positive, then trastuzumab (a monoclonal antibody which targets HER-2 receptor) may be an effective therapy. Hence testing for expression of HER-2 in tumor cells is useful in the management of breast cancer.

Pharmacogenomics is one of the fields in which the Food and Drug Administration (FDA) seems to have a large potential to influence the safety and efficacy of drugs by translating the knowledge on this into regulatory actions like drug labels. To provide guidance to the industry, a final ‘Guidance for industry: pharmacogenomic data submissions’ has been published by FDA. It also offers a new submission path called ‘voluntary genomic data submissions’ to encourage sponsors that are using pharmacogenomics in exploratory research to submit such information for early discussion with the FDA, but without regulatory implications.\(^5\)

Pharmacogenomics can make current and future drugs safer and more effective by targeting them to patients who will benefit the most from them. Only one-third of clinical trials incorporate pharmacogenetics. The combined weight of proven examples whereby pharmacogenetics affects drugs and the possibility of even more examples being elucidated in the coming decades, dictates that pharmacogenetics be incorporated into the drug approval process. Significantly, the knowledge on this into regulatory actions like drug labels. To provide guidance to the industry, a final ‘Guidance for industry: pharmacogenomic data submissions’ has been published by FDA. It also offers a new submission path called ‘voluntary genomic data submissions’ to encourage sponsors that are using pharmacogenomics in exploratory research to submit such information for early discussion with the FDA, but without regulatory implications.\(^6\)

Sir,

Typhoid and paratyphoid fevers are of major public health concern due to the emergence of resistance to fluoroquinolones, the presently recommended first line of therapy. Reports on treatment failure after administration of ciprofloxacin to patients with enteric fever are increasing.\(^7\) Among the nontyphoidal Salmonellae, Salmonella enterica serovar Typhimurium has been reported to show multidrug resistance.\(^8\) The study reports the antibiotic susceptibility profile of Salmonella spp., highlighting the re-emergence of chloramphenicol sensitivity and rising resistance to ciprofloxacin, in addition to the isolation of rare serovars of Salmonella enterica.

Salmonella spp. (n = 124) isolated from 3,956 blood samples of suspected enteric fever cases, collected during August 2003 to July 2006, were included in the study. Serological typing of the isolates was done at the National Salmonella and Escherichia Center, Central Research Institute, Kasauli, India. All the isolates were screened for susceptibility to antimicrobial drugs like amoxycillin, cotrimoxazole, chloramphenicol, cefuroxime, ceftriaxone, ciprofloxacin and nalidixic acid by the disk diffusion method as per Clinical
and Laboratory Standard Institute (CLSI) guidelines. Minimum inhibitory concentration (MIC) of ciprofloxacin and nalidixic acid was determined by the standard broth dilution method according to CLSI (formerly NCCLS) guidelines.

Various *Salmonella enterica* serovars isolated from blood cultures were *S. Typhi* (71), *S. Paratyphi A* (37), *S. Typhimurium* (13), *S. Welteverdine* (01), *S. Bareilly* (01) and *S. Infantis* (01).

All the nontyphoidal *Salmonella* serovars were isolated from immunocompromised patients. All isolates were sensitive to cefuroxime and ceftriaxone, the drugs of choice for ciprofloxacin treatment failures. Drug resistance pattern of the *Salmonella* serotypes is shown in Table 1.

Among the 54 ciprofloxacin-sensitive *S. Typhi* isolates, 15 were sensitive and 39 were resistant to nalidixic acid by the disk diffusion method. Fifteen *S. Typhi* isolates that were sensitive to both nalidixic acid and ciprofloxacin by disk diffusion showed an MIC range of 0.062-0.125 µg/ml for ciprofloxacin. Thirty-nine isolates that were resistant to nalidixic acid and sensitive to ciprofloxacin had an MIC range of 0.25-1.0 µg/ml for ciprofloxacin. MIC of 0.50-2.5 µg/ml was recorded for 13 *S. Typhi* isolates that were categorized as intermediate susceptible to ciprofloxacin by disk diffusion. Two ciprofloxacin-resistant and two intermediately susceptible isolates of *S. Typhi* had an MIC of 4 µg/ml.

Among the 37 *S. Paratyphi A* strains, 25 were sensitive to ciprofloxacin and 3 were sensitive to nalidixic acid by disk diffusion. The ciprofloxacin MIC of sensitive isolates was <0.125 µg/ml, and the intermediately susceptible isolates (n = 12) showed a value between 0.250 and 1.0 µg/ml. Eight isolates of *S. Typhimurium* were sensitive, and five were resistant to nalidixic acid by disk diffusion. Among the ‘nalidixic acid’-resistant strains, 3 were found to be intermediately susceptible to ciprofloxacin by disk diffusion. MIC of intermediately susceptible strains varied from 0.25-1 µg/ml.

The incidence of multidrug resistance (MDR – resistance to three or more antibiotics) in *S. Typhi* strains was 22% in the first year, 7% in the second year and 9% in the third year of the study. MDR was not observed among the isolates of *S. Paratyphi A* and *S. Typhimurium* in the present study.

<table>
<thead>
<tr>
<th>Year</th>
<th><em>Salmonella</em> serovars</th>
<th>No. of strains</th>
<th>Drug resistance pattern</th>
<th>MIC range (µg/ml)</th>
<th>Ciprofloxacin</th>
<th>Nalidixic acid</th>
</tr>
</thead>
<tbody>
<tr>
<td>2003-04</td>
<td><em>S. Typhi</em></td>
<td>23</td>
<td>05 (22%)</td>
<td>A + C + Co</td>
<td>0.062-0.5</td>
<td>16-256</td>
</tr>
<tr>
<td>2004-05</td>
<td><em>S. Paratyphi A</em></td>
<td>08</td>
<td>04l</td>
<td>08 (100)</td>
<td>0.062-1.0</td>
<td>32-256</td>
</tr>
<tr>
<td>2005-06</td>
<td><em>S. Typhi</em></td>
<td>21</td>
<td>01 (5%)</td>
<td>A + C + Co</td>
<td>0.062-0.5</td>
<td>16-256</td>
</tr>
<tr>
<td><em>S. Bareilly</em></td>
<td>01</td>
<td>01</td>
<td>01</td>
<td>01</td>
<td>16</td>
<td>0.156-4.0</td>
</tr>
</tbody>
</table>

MIC of *S. Paratyphi A* isolates varied from 0.25 to 1 µg/ml. The MIC of 16 isolates was 0.062 µg/ml, and three isolates showed a 0.25 µg/ml MIC.

It is interesting to note that there is a gradual increase in the number of strains of *Salmonella enterica* resistant to nalidixic acid (MIC ≥32 µg/ml), and these nalidixic acid resistant strains showed reduced susceptibility to ciprofloxacin (MIC 0.25-1.0 µg/ml). Although the level of reduced susceptibility to ciprofloxacin is below that regarded as clinically significant, an increasing number of treatment failures at this level has been noted. This suggests that current CLSI break point (4 µg/ml) for ciprofloxacin may not accurately predict clinical response to treatment of patients with extra-intestinal salmonellosis.

Two isolates of *S. Typhi* had MIC of 4 µg/ml, which is regarded as typical resistance to ciprofloxacin by CLSI criteria. But by disk diffusion, these isolates were found to be intermediately susceptible. These results clearly show that determination of MIC is necessary for every isolate of *Salmonella*, in order to accurately detect the reduced susceptibility and typical resistance to ciprofloxacin. In the present study, it was found that isolates with reduced susceptibility to ciprofloxacin were resistant to nalidixic acid by disk diffusion. Hence nalidixic acid screening test can be used to detect reduced susceptibility to ciprofloxacin. This will help clinicians to decide on an alternative antibiotic to avoid treatment failures.

Chloramphenicol sensitivity in *S. Typhi* (>90%) has been increasing in different regions of India. As noted in the present study, re-emergence of sensitivity (94.4%) and reduced resistance (5.6%) to chloramphenicol in *S. Typhi* isolates make it essential to reconsider chloramphenicol as the antibiotic of choice for enteric fever in place of ciprofloxacin or third-generation cephalosporins, the present treatment regimen of typhoid fever. There have been very few reports on the isolation of rare serovars like *S. Welteverdine*, *S. Bareilly*, *S. Typhimurium* and *S. Infantis* from blood cultures.

Various antibiotic resistance patterns of the *Salmonella* isolates have been noted. This suggests that current CLSI guidelines, which are susceptible to commonly used antibiotics, might have been isolated. However, even these rare serovars may develop resistance to antibiotics in due course, and the policy of empirical treatment for enteric fever and septicaemia needs to be rationalized.

**ACKNOWLEDGMENT**

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**REFERENCES**

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Meliodosis is an infectious disease caused by gram-negative soil-dwelling bacillus Burkholderia pseudomallei. Synonyms include Pseudoglanders, Vietnamese time bomb, Whitmore’s disease and Rangoon beggar’s disease. Alfred Whitmore and C. S. Krishnaswami first described melioidosis as a ‘glanders-like’ disease in morphia addicts. An extensive literature review has been performed over melioidosis through various search engines such as Pubmed, Embase, Medscape, Altavista and Google. Diagnosis requires a high index of clinical suspicion and is dependent on microbiological confirmation. Prompt treatment with long-term combination antibiotics in high dosages and surgical drainage of abscesses improves survival.

Key words: Burkholderia pseudomallei, melioidosis, musculoskeletal, orthopedics