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QUINOLONES AND THEIR CLINICAL RELEVANCE IN THE MANAGEMENT OF ENTERIC FEVERS IN THE NEW MILLENNIUM: FINDINGS FROM A REVIEW OF 55,853 *SALMONELLA* ISOLATES

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ABSTRACT

The study was set up to review the current susceptibility patterns of *Salmonella* isolates to quinolones. A systematic literature search on in vitro and in vivo susceptibility patterns of *Salmonella* isolates to various quinolones was carried out from relevant published articles over a 25 year interval (1982-2007). Data obtained was analysed using simple descriptive methods. Susceptibility patterns of 55,853 *Salmonella* isolates to quinolones from 845 reports were reviewed. The most active quinolones encountered were (where n= number of *Salmonella* isolates tested): ciprofloxacin, 99%(n=15,432); grepafloxacin, 99%(n=2,701); gemifloxacin, 97%(n=1,209); ofloxacin, 96%(n=8,692); and sparofloxacin, 93%(n=557). This was followed by: enoxacin, 92%(n=2,653); gatifloxacin, 90%(n=788); lomefloxacin, 83%(n=1,823); and levofloxacin, 81%(n=3,228). And the least active quinolones against *Salmonella spp.* were norfloxacin, 76%(n=1,355); pefloxacin, 62%(n=4,307); and nalidixic acid, 61%(n=17,542). Quinolones at present have been found to be quite effective in the management of enteric fever and their use should be sustained. However, susceptibility patterns of the local *Salmonella* isolates should be conducted to identify the most appropriate quinolone to use in this environment. Furthermore, in the absence of a susceptibility report, ciprofloxacin, grepafloxacin, gemifloxacin, ofloxacin, and sparofloxacin may be considered preferred choices on proven diagnosis of enteric fever.

KEY WORDS: Quinolones, Enteric Fevers, Treatment, New Millennium

INTRODUCTION

Quinolones are synthetic analogs of nalidixic acid and act by inhibiting bacterial DNA synthesis by blocking the enzyme DNA gyrase. They are presently grouped into four generations which include members such as, nalidixic acid, lomefloxacin, clinafloxacin and moxifloxacin as examples of first, second, third, and fourth generations respectively.

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Among the antimicrobials presently available for the treatment of enteric fever, preferences for quinolones among clinicians appear to be on a steady increase. About 16 million cases of enteric fever are reported globally with over 600,000 deaths yearly (Karinki, *et al*, 2004). Over 75% of the cases occur in sub-Saharan Africa, South east Asia, the Mediterranean, and parts of central and south America (Meltzer, *et al*, 2005; and Ekdahi, *et al*, 2005).

There have been varying reports on the susceptibility patterns of *Salmonella* isolates to various quinolones globally. Findings from Lagos, Nigeria, showed a 100% activity of both ciprofloxacin and ofloxacin and 60% nalidixic acid against *Salmonella spp.* tested (Akinyemi, *et al*, 2000). In Kumba, Cameroun, on the other hand, treatment failure from ciprofloxacin was recorded (Nkemngu, *et al*, 2005), while in Cairo, Egypt, a high nalidixic acid activity (over 90%) was recorded (Wasfy, *et al*, 1996); however, in India and Pakistan, resistance of *Salmonella spp.* to nalidixic acid, ciprofloxacin and other quinolones was found to be on the increase (Chandel, and Chaudhry, 2001).

Multidrug resistant *Salmonella typhi* (MDRST) has been on a steady increase over the past two decades and has since assumed a global dimension (Mermin, *et al*, 1998; and Caumes, *et al*, 2001). This is reported to have began with the emergence of resistance to chloramphenicol in the late 1980s after serving for over 40 years as the drug of choice (Rowe, *et al*, 1997; and Shanehan, *et al*, 1998). In Srinagar-Kashmir, India a very rare strain of *S. typhi* phage biotype II untypeable (UVS_2) was recovered from an outbreak of enteric fever and was resistant to all the antimicrobial agents tested except norfloxacin (Kamili, *et al*, 1993). Also in Moscow, Russia, in an epidemiological survey, no single antimicrobial agent was found to have absolute (100%) activity against the *Salmonella* isolates tested (Makhnev, 2003). Similarly, in Lagos, Nigeria, 25 of 41(61%) isolates of *Salmonella spp*. from cases of pyrexia of unknown origin (PUO) were found to be resistant to all the antimicrobials tested (Akinyemi, *et al*, 2005). In like manner, a laboratory-based surveillance of *Salmonella serotype typhi* infections in the United States showed that 74(24%) were resistant to 1 or more antimicrobial agents, while 51(17%) were resistant to 5 or more agents, including ampicillin, chloramphenicol, and trimethoprim-sulfamethoxazole (MDRST) (Ackers, *et al*, 2000).

With the proper treatment of enteric fever progressively becoming a serious challenge among health personnel due to the increasing and widespread resistance of the organisms to the common drugs (Mirza, *et al*, 2000; Rahman, *et al*, 2002; Price, *et al*, 2001; and Arad, *et al*, 1996); and with the varying reports on the susceptibility patterns of *Salmonella spp.* to various quinolones across the globe, a general review of the usefulness of this group of drugs in the treatment of enteric fevers becomes a worthwhile venture.

Furthermore, in the present scenario where *Salmonellae* appear to be winning the antimicrobial war (Nkemngu, *et al*, 2005; Chandel, *et al*, 2001; and Ackers, *et al*, 2000), a periodic review of its antibacterial activity becomes necessary. Such information would be a veritable tool for clinicians who, either for time constraint or for lack of adequate facilities may not afford to rely on a comprehensive susceptibility report prior to commencement of treatment.

MATERIALS AND METHODS

A systematic literature search on antimicrobial susceptibility pattern of *Salmonella species* to quinolones was undertaken on published articles for a 25 year interval (1982-2007). This consists of articles on *in vitro* antimicrobial susceptibility pattern of individual isolates of *Salmonella typhi* and *Salmonella paratyphi* to quinolones in various research centres across the globe.

Data compiled was comprised of relevant reports from original articles, review articles, short communications and letters to the editors. The *In vitro* susceptibility results were standardized by collating findings from studies whose methodologies were based on the diffusion and dilution methods of National Committee for Clinical Laboratory Standards (NCCLS) protocol. Similarly, monotherapy results from *In vivo* susceptibilities whose interpretations were based on both the bacteriological and clinical outcomes of the patients were compiled. Data obtained were analysed using simple descriptive methods.

RESULTS

The antimicrobial susceptibility pattern of 55,853 strains of *Salmonella spp.* from 845 reports were reviewed with varying number of isolates tested per specific quinolone.

Salmonella spp. on the average were found to be most susceptible to (where n= number of *Salmonella* isolates tested) ciprofloxacin, 99% (n=15,432); grepafloxacin, 99% (n=2,701); gemifloxacin, 97% (n=1,219); ofloxacin, 96% (n=8,692); and sparofloxacin, 93% (n=557). This was followed by enoxacin, 92% (n=2,653); gatifloxacin, 90% (n=788); lomefloxacin, 83% (n=1,823); and levofloxacin, 81% (n=3,228). The least sensitive quinolones against *Salmonella spp.* were found to be norfloxacin, 77% (n=7,277); moxifloxican, 76% (n=1,355); pefloxacin, 62% (n=4,303); and nalidixic acid, 61% (n=17,542)

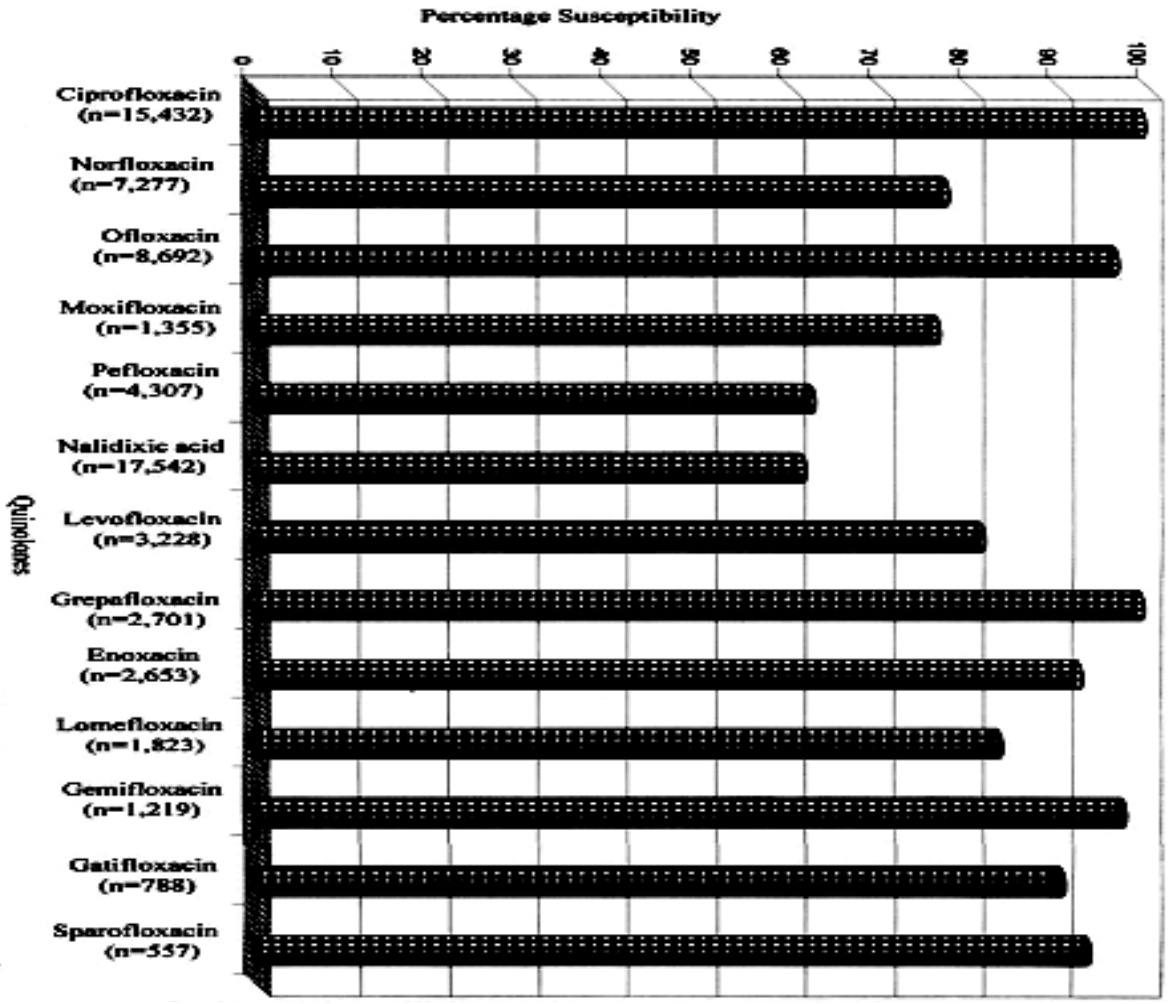

Fig. 1: Susceptibility patterns of 55,853 strains of *Salmonella species to* quinolone from 845 reports (n= number of isolates tested)

DISCUSSION

Ciprofloxacin, grepafloxacin, gemifloxacin, ofloxacin, and sparofloxacin were on the average found to be 99%, 99%, 97%, 96%, and 93% active respectively against the 55,853 *Salmonella spp.* reviewed. This varies from the 23.5% ciprofloxacin resistance recorded in Thailand on 1,210 *Salmonella* isolates (Hakanen, *et al*, 2001), to the 99.5% susceptibility to ciprofloxacin, ofloxacin and gemifloxacin recorded in Beijing, China (Jiang, *et al*, 1997), and the 100% sensitivity recorded in Port Harcourt, Nigeria (Ibe, and Wariso, 1996) and Vienna, Austria (Graninger, *et al*, 1996). In Saskatoon, Canada, the activity of gemifloxacin against *Salmonella spp*. and other *Enterobacteriaceae* was found to be enhanced over that of ciprofloxacin whose activity was significantly higher than that of chloramphenicol, cotrimoxazole, ampicillin, gentamicin and several cephalosporins (Bloneau, *et al*, 2003). In Japan, *Salmonella spp.* were found to be over 98% susceptible to sparofloxacin (Ohnishi, *et al*, 2000).

The 56.6% chloramphenicol, 70% ampicillin, 50.0% amikacin, 43.3% gentamicin, and 40.0% ampicillin resistance of *Salmonella spp.* as against 0% to ciprofloxacin and ofloxacin as recorded in Rajasthan further proves the therapeutic edge quinolones have over these antityphoid drugs (Maheshwari, and Agarwal, 1996). In Germany, grepafloxacin was found to have similar antityphoid properties with ciprofloxacin which was in it self over 97% active (Dalhoff, and Schmitz, 2003).

The activities of lomefloxacin, levofloxacin, gatifloxacin and enoxacin were on the average moderate among the *Salmonella spp*. reviewed (81%-92%). In Tokyo, Japan, the activity of levofloxacin and a newer quinolone, DK-507K against *Salmonella* and other *Enterobacteriaceae* were found to be high and comparable to that of ciprofloxacin, while DK-507K was highly active against ciprofloxacin resistant strains (Otani, et al, 2003). A large scale multi-centre clinical trial of DK-507K may be required to establish its suitability in view of its pharmacodynamic advantages over ciprofloxacin in the treatment of enteric fevers.

In France, in a study on 2,819 bacterial strains lomefloxacin and pefloxacin were found to have similar activity to ciprofloxacin (Soussy, *et al*, 1990). They however showed expanded activity against organisms such as *Staphylococci, Clostridium perfringens, Bacteroides fragilis* and *Branhamella*. Also in New Zealand, lomefloxacin, besides having high antimicrobial properties comparable to ciprofloxacin, it was found that, it can conveniently be taken once a day with the same therapeutic outcome, thus enhancing compliance (Wadworth, *et al*, 1991). In Poland, the activity of enoxacin against 362 clinical bacterial isolates was found to be about half that of ciprofloxacin but several folds higher than that of the penicillins and many second and third generation cephalosporins used in typhoid treatment (Reeves, *et al*, 1984).

The activity profile of norfloxacin, moxifloxacin, pefloxacin, and nalidixic acid were on the average comparatively lower (61%-77%). These drugs on individual basis have still been found to be up to four times more active than drugs such as amoxicillin, ampicillin, chloramphenicol, cotrimoxazole and gentamicin, drugs commonly used in the treatment of typhoid fevers (Caumes, *et al*, 2001; Rowe, *et al*, 1997; Shanehan, *et al*, 1998; and Kamili, *et al*, 1993). The over 96% norfloxacin activity recorded in New York, USA (Cunha, *et al*, 1997); and the over 90% *In vivo* activity of moxifloxacin, getofloxacin and grepafloxacin in Germany (Lubasch, *et al*, 2000); and the 21.6% and 12.1% resistance of two different strains of *Salmonellae* against nalidixic acid in Seoul, South Korea (Choi, *et al*, 2005), further illustrate the widespread regional and geographic distribution of the resistance

patterns of *Salmonella spp*. globally. Quinolones, though generally active against *Salmonella spp.*, activity patterns of individual drugs on local isolates should be known to aid efficient patient management.

The sub-therapeutic bioavailability commonly associated with administration of nalidixic acid renders it ineffective in the treatment of enteric fevers. Its usefulness in predicting the susceptibility pattern of *Salmonella spp*. to other quinolones has well been documented in studies from Rawalpondi, and Karachi, Pakistan (Anjum, *et al*, 2004; and Zafar, *et al*, 2005), Tuku, Finland (Ray, *et al*, 2006) and Chandigah, India (Hakanen, *et al*, 1999). This susceptibility indicator would aid in timely prescription of newer quinolones, especially in the developing countries where facilities for susceptibility testing of the new drugs may be lacking.

The antityphoid properties of other quinolones such as temafloxacin, tosufloxacin, sitafloxacin and trovafloxacin also need to be ascertained so as to establish their usefulness in the treatment of enteric fever.

In conclusion, this study has shown that, quinolones are at present considerably effective in the treatment of enteric fevers and their use should be sustained. They could also be a solution to the present rise in multidrug resistant *Salmonellae* (MDRS). Their choice should however be based on the antimicrobial susceptibility pattern of the local *Salmonella* strains so as to enhance efficient enteric fever therapy. Generally, ciprofloxacin, grepafloxacin, gemifloxacin, ofloxacin and Sparofloxacin may be considered on diagnosis of enteric fever in the absence of a reliable susceptibility report.

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