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# Evaluation of Antimicrobial Activity of a Novel Non Antibiotic: The Tetracyclic Antidepressant Drug Mianserin

**Bidisha Ghosh[1], Jette E Kristiansen[2], Shauroseni Palchoudhuri[3], Debalina Sinha Roy[3], Sukhen Das[1] and Sujata G Dastidar[3]***

*[1]Department of Physics, Jadavpur University, Kolkata, West Bengal, India*

*[2]Memphys Centre for Biomembrane Physics, Department of Physics and Chemistry, University of Southern Denmark, Odense, Denmark*

*[3]Department of Microbiology, Herbicure Healthcare Bio-Herbal Research Foundation, Saral Dighi (E), Boral, Kolkata, West Bengal, India*

***Corresponding Author**: Sujata G Dastidar, Department of Microbiology, Herbicure Healthcare Bio-Herbal Research Foundation, Saral Dighi (E), Boral, Kolkata, West Bengal, India.

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## Abstract

The use of antibiotics and antibacterial chemotherapeutics has become more and more restricted due to the emergence of drug resistant bacteria which makes some of the most broad spectrum antibiotics ineffective. This resulted in search for antimicrobial activity in pharmacologically diverse groups of drugs and the most active compounds were found to the tricyclic phenothiazines and also those that were structurally related to phenothiazines. Such drugs possessing antimicrobial activities are termed as non-antibiotics. The antidepressant drug mianserin being structurally closely related to phenothiazines was selected to determine its antimicrobial properties. Mianserin was found to exhibit a definite antimicrobial property against 166 strains of bacteria belonging to 3 Gram positive and 6 Gram negative genera. The minimum inhibitory concentration (MIC) was determined with the help of agar diffusion technique by following the guidelines of Clinical and Laboratory Standards Institution. The MIC ranged from 5 to 25 µg/ml in most of the strains; however, it may be mentioned here that a few bacteria were inhibited even at lower concentrations. The drug was found to be bacteriostatic against *Staphylococcus aureus* as well as *Vibrio cholerae*. In the animal experiments mianserin was found to produce significant protection ($P < 0.001$) at a rather low dose (20 µg/ mouse) in the Swiss albino male mice that were challenged with 50 medial lethal dose of the known mouse virulent bacterium *Salmonella enterica* serovar Typhimurium. Additionally the drug was able to reduce the number of viable bacteria in blood and organ homogenates of mice treated with mianserin. Therefore mianserin has definite possibilities for being developed as a novel antimicrobial agent.

***Keywords:*** *Antidepressant; Mianserin; Non-Antibiotic; Bacteriostatic; Tetracyclic Compound*

## Introduction

Looking back to the history of human ailments, infectious diseases have accounted for a very large proportion of diseases as a whole. To combat the battle against the infectious diseases, a large number of antibiotics and antimicrobial chemotherapeutics are now available from numerous medium to very large pharmaceutical industries throughout the world. However, extensive abuse of such broad spectrum antibiotics largely attributes to the emergence of multidrug resistance factors among microbial pathogens. Such a phenomenon in the chemotherapeutics is often coupled with the toxicity possessed by many antimicrobials. This incessant problem had urged several researchers around the world to involve themselves in studies to explore newer drugs with lesser degrees of toxicity and possibly fewer chances of developing resistance. Hence there was an intensive search for newer antimicrobial agents that can overcome these drawbacks [1-5]. Among already existing pharmaceutical compounds that are not categorized as antimicrobials, scientists from different parts of the world started reporting on detection of moderate to powerful activity against pathogens in many such compounds. Examples include an-

tihistamines like bromodiphenhydramine and diphenhydramine, methdilazine, promethazine and fluphenazine, antipsychotic agents like chlorpromazine, promazine, thioridazine, clopenthixol, flupenthixol, trifluoperazine, triflupromazine, amitryptiline, ferroxotine and imipramine, anti-hypertensives like propranolol and methyl-DOPA, anti-inflammatory agent like diclofenac sodium, anti-cholinergic agent like dicyclomine hydrochloride, some of the cardiovascular agents, antispasmodic drugs and even local anaesthetics [1,6-35]. All such compounds having antimicrobial properties in addition to their already existing pharmacological actions have been grouped together and christened "non-antibiotics" [36-38]. Such studies open up possibilities of discovering new molecules to treat problematic infections. However, none of the marketed drugs under the anti-depressant category has not yet been explored for such a function. On the basis of understanding of multiplicity of actions in chemically synthesized drugs, this present study has been designed to carry out elaborate and standard *in vitro* and *in vivo* tests to prove the antimicrobial efficacy in the antidepressant mianserin hydrochloride.

## Materials and Methods

### Bacteria

A total of 166 different bacteria belonging to both Gram positive and Gram negatives types were tested. Some of the strains were obtained from National Collection of Type Cultures (NCTC), London and American Type Culture Collection (ATCC), USA; others were isolated as human pathogens in Kolkata as well as different parts of India. The isolates were identified by the methods of Collee., *et al*. [39] and were preserved in freeze-dried state and also as stab-slant cultures.

### Drug

The pure dry powder of mianserin HCl was purchased from Sigma Chemicals, Copenhagen, Denmark and preserved at 4°C. The drug was soluble in water and remained stable in aqueous solution. The molecular weight of the drug is 264372 and its formula is $C_{18}H_{20}N_2$; its structure is shown in figure 1.

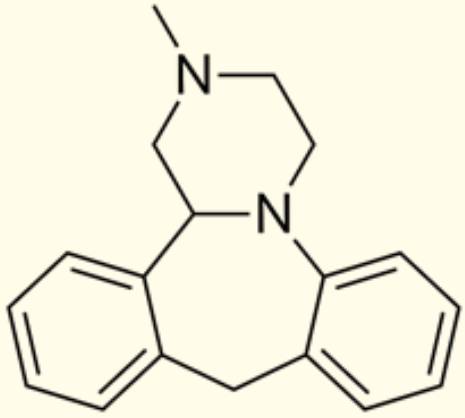


***Figure 1:*** *The chemical structure of mianserin.*

### Media

Liquid media used were peptone water (PW, prepared with 1% bacteriological peptone, Oxoid, UK, plus 0.5% Analar NaCl), nutrient broth (NB, Oxoid) and Muller Hinton Broth (MHB, Oxoid). Solid media were nutrient agar (NA, Oxoid) and Muller Hinton agar (MHA, Oxoid). The pH of all the media were maintained at 7.2 -7.4.

### *In vitro* screening of mianserin for determination of its minimum inhibitory concentration (MIC)

MIC of mianserin against different test bacteria was determined following the standard guidelines of agar diffusion technique as de-

scribed by the Clinical Laboratories and Standards Institute [40]. The drug was dissolved in sterile distilled water and added to molten NA/MHA at concentrations of 0 (control), 5, 10, 25, 50 and 100 µg/ml. These were then poured into sterile Petri dishes maintaining the pH.

Gram positive bacteria were grown in NB/MHB and Gram negative bacteria were cultivated in PW for 18 hours. These were then harvested during the stationary phase. A suspension of every organism was prepared in 5 ml of sterile distilled water and the turbidity was adjusted to 0.5 McFarland standard with the help of UV-VIS Spectrophotometer (Evolution 201, Thermo Scientific) which corresponded to 2.4 x $10^8$ colony forming units (CFU)/ml. The inocula were diluted further with sterile distilled water in such a manner that a 2mm internal diameter loopful of culture contained $10^5$ CFUs. Such cultures were spot inoculated on plates containing NA/MHA (control) and increasing amounts of the agent. Presence or absence of growth was noted after 24h incubation at 37°C, incubation was extended upto 72h where necessary.

**Mechanism of antibacterial action of mianserin**

The bacterial strain highly sensitive to mianserin, namely *S. aureus* 8532 was selected. The strain was grown in 4 ml NB for 18h. Then, 2 ml of this culture was added to 4 ml of fresh NB and incubated at 37°C for 2h to help the strain attain logarithmic growth phase. At this stage, the CFU count was determined and mianserin was added at a concentration that was double the amount of the MIC value against the selected sensitive strain. Thereafter CFU counts from the culture was individually taken after 2, 4, 6, 8 and 18h after addition of the drug. In an identical manner the pattern of action of *V. cholerae* 569 B was determined.

**Validation of the potency of the drug through *in vivo* tests**

This was performed in 3 - 4 weeks old Swiss white male mice, each weighing 18 - 20g following standard guidelines [41,42]. Throughout the entire period of this experiment all the animals were kept in the standard conditions of temperature at 24 ± 1ºC, relative humidity of 50 - 60% with a photo period of 14:10h of light: darkness. Water and dry pellets were given to the mice *ad libitum*. The mouse virulent bacterium *Salmonella enterica* serovar Typhimurium NCTC 74 was routinely given as the challenge for all the tests. The challenge dose was the same as described earlier; it was 0.95 x $10^9$ CFU of the mouse passaged strain *S. enterica* 74 suspended in 0.5 ml NB [8]. Reproducibility of the challenge dose was ensured by standardizing its optical density at 640 nm in a UV-VIS spectrophotometer (Evolution 201, Thermo Scientific) to obtain the desired CFU on NA/MHA.

To determine the toxicity of mianserin, a total of 40 mice were taken. Of these, 20 were injected with 10 µg of the drug and the remaining 20 received 20 µg of mianserin. These animals were then kept under observation for up to 100h.

Two groups of mice, with 20 animals per group were kept in separate cages. Group I was administered intraperitoneally 10 µg of mianserin per mouse (0.5 ml from 1000 µg/ml solution), whilst Group II received 20 µg the agent per mouse (0.5 ml from 2000 µg/ml solution). After 3h, both groups were challenged with 50 MLD of *S. enterica* NCTC 74. A control group of 60 mice was also injected similarly with the same bacterial strain and 0.1 ml sterile saline instead of the drug. The protective capacity of the drug was determined by recording the mortality of the mice in different groups for up to 100h of treatment. Results were compared statistically by $\chi^2$ test.

In another experiment, two groups of mice, with five animals per group, were taken. Group I was administered 20 µg of mianserin and Group II was given 0.5 ml sterile saline. After 3h, both groups were given a 50 MLD challenge of *S. enterica* NCTC. After 18 h, all the animals were sacrificed. Their heart blood was collected aseptically and serum was separated individually; then their livers and spleens were removed aseptically and homogenized in tissue homogenizers under sterile condition. CFU counts of the individual organs were determined separately. Statistical analysis of the *in vivo* data was done by Student's t-test.

## Results

**Antibacterial activity of mianserin by *in vitro* screening**

*In vitro* antimicrobial potentiality of mianserin is presented in table 1. Among 4 strains of *Bacillus* spp. only 1 strain was inhibited at 10

µg/ml concentration and the remaining 3 were unable to grow at 25 µg/ml of mianserin. Out of 31 strains of *S. aureus* 12 failed to grow at 5 µg/ml amount of mianserin, 8 strains were inhibited at 10 µg/ml concentration, 5 at 25 µg/ml and the remaining 6 at 50 µg/ml of the drug. Only 2 strains of *L. monocytogenes* were taken in this study, 1 of this was inhibited at 5 µg/ml concentration and the other at 10 µg/ml amount. Among Gram negative organisms results of 19 strains of *E. coli* showed inhibition of 2 strains at 5 µg/ml, 4 strains at 10 µg/ml, 2 at 25 µg/ml and the remaining 11 at 50 µg/ml of mianserin. Strains of *Salmonella* and *Shigella* revealed similar pattern of inhibition much like those of *E. coli*. Isolates belonging to *K. pneumoniae* were far less sensitive; out of 9 strains tested 4 were inhibited at 50 µg/ml, 3 at 100 µg/ml while the other two remain uninhibited even at 100 µg/ml of mianserin. Out of a total of 36 *V. cholerae*, 4 strains failed to grow at 5 µg/ml, 10 at 10 µg/ml, 14 at 25 µg/ml and the remaining 8 at 50 µg/ml of the drug. *P. aeruginosa* appeared to be fairly resistant to this drug since out of 12 isolates, 4 strains were unable to grow at 50 and 100 µg/ml concentration of mianserin while the remaining 4 were resistant. Thus among both *K. pneumoniae* and *P. aeruginosa* no isolate could be inhibited up to 25 µg/ml of mianserin.

| Bacteria | No. tested | No. of strains inhibited by Mianserin (µg/ml) | | | | | |
|---|---|---|---|---|---|---|---|
| | | 5 | 10 | 25 | 50 | 100 | > 100 |
| *Bacillus* spp. | 4 | | 1 | 3 | | | |
| *Staphylococcus aureus* | 31 | 12 | 8 | 5 | 6 | | |
| *Listeria monocytogenes* | 2 | 1 | 1 | | | | |
| *Escherichia coli* | 19 | 2 | 4 | 2 | 11 | | |
| *Salmonella* spp. | 25 | 3 | 1 | 14 | 6 | 1 | |
| *Shigella* spp. | 28 | 3 | 2 | 16 | 7 | | |
| *Klebsiella pneumoniae* | 9 | | | | 4 | 3 | 2 |
| *Vibrio cholerae* | 36 | 4 | 10 | 14 | 8 | | |
| *Pseudomonas aeruginosa* | 12 | | | | 4 | 4 | 4 |
| Total | 166 | 25 | 27 | 54 | 46 | 8 | 6 |

***Table 1:*** *In vitro antimicrobial activity of Mianserin.*

Therefore, out of a total of 166 bacterial strains tested, 15% were inhibited at 5 µg/ml of mianserin, 16.3% at 10 µg/ml, 32.5% at 25 µg/ml, 27.7% at 50 µg/ml, 4.8% at 100 µg/ml, while 3.6% turned out to be totally resistant to the test compound.

**Bacteriostatic action of mianserin**

The MIC of mianserin against *S. aureus* NCTC 8532 and *V. cholerae* 569B was determined to be 10 µg/ml. At the logarithmic growth phase of the cultures the CFU counts of the strains were $2.9 \times 10^8$ and $5.4 \times 10^8$ respectively. At this stage 20 µg/ml (double the MIC) of mianserin was added to each culture. Subsequently CFU counts of both the cultures were determined at 2hr intervals. For *S. aureus* NCTC 8532 the CFUs were $2.2 \times 10^6$ after 2hr, $3.6 \times 10^4$ after 4hr, $4.5 \times 10^2$ after 6 hr, $2.8 \times 10^2$ after 8 hr and $2.4 \times 10^2$ at the end of 18hr (Figure 2). Similar bacteriostatic effect of mianserin was observed in *V. cholerae* 569B (Figure 3).

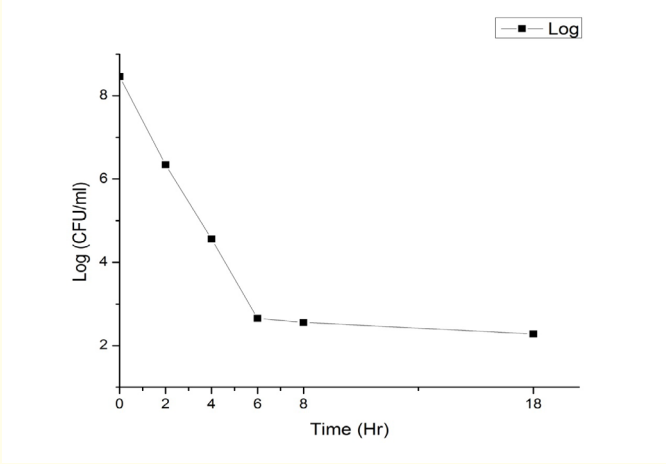


***Figure 2:*** *Bacteriostatic action of 10 µg/ml mianserin on Staphylococcus aureus NCTC 8532 (minimum inhibitory concentration of 5 µg/ml).*

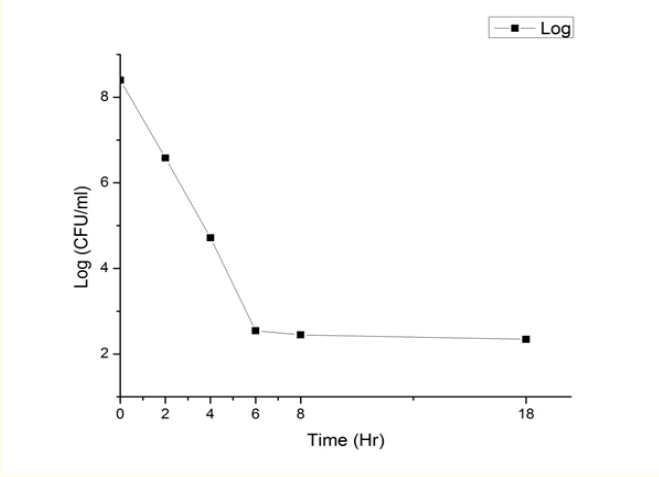


***Figure 3:*** *Mechanism of action of 10µg/mL of mianserin on Vibrio cholerae 569B (minimum inhibitory concentration of 5 µg/mL).*

**Animal experiments**

The results presented in table 2 show when 60 mice were challenged with the virulent *Salmonella enterica* NCTC 74 48 animals died within 100 hr. However, the batches that received mianserin plus the challenge there was definite protection; the batch that received 10µg of the drug 12 out of 20 mice died while the batch that was given 20 µg of mianserin only 3 animals expired. The difference between the drug treated and control was significant according to $\chi^2$ test since $P < 0.05$ in the batch that received 10 µg while $P < 0.001$ in the batch that received 20µg of mianserin (Table 2).

The data presented in table 3 shows that the batch that was given saline in place of the drug the number of viable bacteria (CFU) varied between $4.7 \times 10^7$ and $1.2 \times 10^9$. On the other hand the batch that received the drug mianserin along with the challenge CFU count was significantly reduced in heart blood, liver and spleen after 18hr; the CFU counts were found to vary between $2.2 \times 10^3$ and $8.8 \times 10^4$. Statistical analysis showed $P < 0.01$ for 18hr samples.

| Group | Agent injected per mouse | Mice died |
|---|---|---|
| Control (N = 60) | 0.5 ml sterile saline | 48 |
| Group I (N = 20) | 10 µg Mn | 12* |
| Group II (N = 20) | 20 µg Mn | 3** |

***Table 2:*** *Determination of the in vivo efficacy of Mianserin HCl (Mn) in mice receiving challenge dose of 0.95 x $10^9$ colony forming units of Salmonella enterica serovar Typhimurium NCTC 74 in 0.5 ml nutrient broth.*

*None of the animals died when 10 µg or 20 µg of the drug alone was injected to two separate groups of mice (20 mice in each group).*

**P < 0.05 according to $\chi^2$ test*

***P <0.001 according to $\chi^2$ test*

| Group | No. of mice tested | Drug (µg/mouse) | Cfu /ml | | |
|---|---|---|---|---|---|
| | | | Heart blood | Liver | Spleen |
| I | 5 | Mn 20 | 2.2 X $10^3$ to 4.6 x $10^4$ | 6.1 X $10^3$ to 8.8 x $10^4$ | 1.8 X $10^4$ to 6.5 x $10^4$ |
| II | 5 | Saline (control) | 7.92 X $10^7$ to 1.2 x $10^9$ | 3.82 X $10^8$ to 9.4 x $10^8$ | 4.7 X $10^7$ to 7.9 x $10^8$ |

***Table 3:*** *Reduction in colony forming units (CFU) of S. enterica serovar Typhimurium NCTC 74 at 18h after treatment with Mianserin HCL (Mn) in heart blood , spleen and liver homogenates of mice*

**CFU counts between two group significant P < 0.01 in 18h samples following Student's 't' test (at 1% level of significance).*

## Discussion

The antidepressant agent was found to possess distinctly powerful antibacterial action both *in vitro* and *in vivo* in experimental mice. The sensitive bacteria belonged to members of *Bacillus, S. aureus* and *V. cholerae.* However, 3 out of 9 strains of *K. pneumoniae* and 4 out of 12 strains of *P. aeruginosa* were unable to grow at 50 µg/ml of mianserin. This appears to be a unique phenomenon since strains belonging to these two bacteria exhibit high levels of resistance against majority of the non-antibiotics reported so far by many microbiologists working in this area [2,25-27,31,43,44]. Mianserin was found to possess bacteriostatic activity *in vitro* to both Gram positive and Gram-negative organisms. The protective ability of the drug could be assessed in the mouse model developed in the laboratory, when the animals were challenged with a highly virulent strain of *S. enterica* serovar Typhimurium. The observed data were statistically significant. Mianserin was found to be totally non-toxic at the dosages of both 10 µg/mouse and 20 µg/mouse, but the protection offered by the drug was more significant when the amount of mianserin was 20 µg/mouse. Furthermore, as an antidepressant agent mianserin is administered to patients for long periods covering months and even years. However, it needs to be pointed out here that the antibacterial protection offered by this drug in mice challenged with a virulent organism was obtained only after application of a single dose. It may be pointed out here that Sadik., *et al.* [45] in an intensive study with 16 different psychotropic drugs observed antimicrobial action *in vitro* in mianserin.

Intensive studies carried out by various researchers on phenothiazines revealed that their antibacterial function may probably be linked to the methyl thio substitution at position 2 of the basic phenothiazine ring [46]. Since the structure of this antidepressant drug is largely similar to that of a phenothiazine except for the presence of 4 complete rings in this compound while the latter is tricyclic. Mianserin contains azepine ring as well as pyrazine ring apart from two benzene rings, while a phenothiazine contains two benzene rings plus one thiazine ring. Increased antimicrobial activity in mianserin may possibly be due to the presence of azepine and pyrazine rings.

Mianserin is given to patients suffering from major depression associated with anxiety and agitation. It is also used for enuresis. Most of these disorders are seen frequently among elderly patients, although there are young men and women complaining about depression

all over the world particularly fairly rich people of highly developed countries. These patients are treated with mianserin for long periods, like months and even years. Since the present study has proved beyond doubt that mianserin is a competent antimicrobial agent, patients receiving this drug are doubly benefitted. As this drug is in routine therapeutic usage overcoming all pharmacological barriers mianserin will hopefully be developed as the second or even the first line of antibacterial drug against many infections. Pharmaceutical industries may not be able to label mianserin as an anti-infective agent immediately, but with this background knowledge they are in a position to improve antimicrobial potency by making some minor alterations in its structure and giving it a new name. Thus, structural modifications and clinical or chemotherapeutic synergistic combinations of this drug with known antimicrobial agents including other non-antibiotics may lead to discovery of a novel potent new group of antimicrobial drug.

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**Volume 11 Issue 6 September 2017**