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Review Article

Using pharmaceutical nano-stabilizers to overcome Antimicrobial Resistance

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Abstract

Increasing incidences of Antimicrobial Resistance (AMR) globally, demand that medicines` efficacies and patients` immunity be improved for treatments to achieve ≥ 95% infections` reduction so that post-treatment immunity completes their termination, leaving none that may develop resistance. Improving efficacies also reduces doses used on food-animals and their side effects, for drug-residues in human foods from animals to reduce (AMR-preventive measure) while patients` immunity improves. To test these hypotheses, Medicinal synthetic Aluminum magnesium silicate® (MSAMS), a brand of Aluminum magnesium silicate (pharmaceutical nano-stabilizer), was incorporated to Piperazine, Ampicillin, Chloroquine and Sulfadimidine (to prolong their high-bioavailability time and enhance their delivery) for their efficacies to improve. Piperazine`s and Ampicillin`s recommended dosages reduced 82.94% and 80.68% of sensitive Helignosomoides bakeri infestation and *Salmonella gallinarum* infection, respectively (cure: ≥ 80.00%-reduction), while their 75% dosages in MSAMS, reduced 96.82% of the helminth and 97.84% of the bacterium (termination). Supporting 75% dosages of MSAMS-formulated Ampicillin, Sulfadimidine and Chloroquine with antioxidants cured Ampicillin-resistant *E. coli* (95.70%), Sulfadimidine-resistant *E. coli* (84.34%) and Chloroquine-resistant Plasmodium berghei (100%) infections. We conclude that tagging pharmaceutical nano-stabilizers to antimicrobials and treating with their 75% dosages, supported with antioxidants overcome AMR.

Keywords: Prolonging High-Bioavailability Time; Enhancing Delivery; Reducing Side-Effects

Introduction

In recent times, development of resistance against Antimicrobials used for treatments by microorganisms that cause diseases in animals and in human-beings, has been on the increase [1]. This is a major challenge to medical practice, all over the world [2]. To prevent development of resistance by infections against drugs, treatments should reduce loads of infections by at least 95% [3]. When more than 5% of loads of infections are left after treatments, body`s immune responses may not be able to complete elimination of such infections and infections that survive treatments start developing resistance against medicines used [3]. Problem of antimicrobial resistance is made worse by the practice of adding antimicrobials to feeds of animals as growth promoters. This leads to development of resistance by pathogens that infect animals and when the resistant infections find their way into the human food-chain, they transfer the resistance to pathogens that infect human-beings [5]. It has been reported that over 80% of cases of cystitis in human-beings were due to *E. coli* infections contracted from animals. Also, when high doses of drugs are used to treat food animals, high concentrations of residues of the drugs could be passed to human-beings who eat meat, milk or eggs of the animals. This also leads to development of resistance by microorganisms that infect human-beings, because of constant exposure to sub-therapeutic doses of the drugs. Need therefore exists to search for pharmaceu-

ticals that could be formulated to antimicrobials to improve their efficacies both for veterinary treatments and for treating human-beings.

When in suspension, nanoparticles of molecules of Aluminum magnesium silicate (AMS), an approved pharmaceutical stabilizing agent, form three dimensional colloidal structures round other substances in the suspension [4]. By that mechanism, AMS stabilizes medicines. When stabilized, medicines are protected from being rapidly metabolized. Time of high bioavailability of the medicines is thus prolonged. When time of high bioavailability of medicines is prolonged, their efficacies improve. Also, nanoparticles enhance delivery of medicines to targets and across physiological barriers [6]. So, AMS may in addition to prolonging time of high bioavailability of Antimicrobials, enhance their delivery to targets and across the blood-brain barrier and other physiological barriers. Every medicine has both its desired effects and its side effects. Most Antimicrobials cause immune-suppression when used at high dosages. To protect immune systems of treated animals against immune suppression from medicines and to enhance their responses against infections, antioxidants which include the B-vitamins and high levels of Vitamins A, C, E and Selenium in feed of animals are used.

Some countries do not have AMS as mineral deposits but they may have two other medicinal minerals, Aluminum silicate (AS) and Magnesium silicate (MS). So, AS and MS were reacted to produce a brand of AMS that was named, Medicinal synthetic AMS® {MSAMS®: $Al_4(SiO_4)_3+3Mg_2SiO_4 \rightarrow 2Al_2Mg_3(SiO_4)_3$} [4]. Dextrose monohydrate, a simple sugar was incorporated in MSAMS®, to convey the electrically charged nanoparti*cles*, by aided transport, across mucous membranes of stomach and intestines of treated patients into blood-circulation [7]. Formulations of the MSAMS® and Ampicillin trihydrate, Piperazine citrate, Sulfadimidine and Chloroquine phosphate were tested on sensitive and resistant infections.

Efficacy-trials with animals

Four groups, each of 10 randomly selected chicks, infected with *Salmonella gallinarum* were treated with Ampicillin trihydrate (AT) for 5 days. Two groups were treated at dose rates of 10 mg and 7.5 mg of AT per Kg body weight respectively, with 100% Ampicillin. Two other groups were similarly treated with Ampicillin-MSAMS® formulation. The fifth group served as control. Bile of 5 chicks from each group was harvested. Then 0.1 ml of bile from each chick was added to 0.9 ml of normal saline to get a 1:10 dilution. Again 0.1 ml of the 1:10 bile-dilution was added to 0.9 ml of normal saline to make a 1:100 dilution. Finally, 0.05 ml of each diluted bile was plated on Mc-Conkey agar and incubated at 37˚C for 24 hours. The *S. gallinarium* colonies (X) were counted and expressed as colony forming units per ml (CFU/ml) by the formula: CFU/ml = x/5 × 10,000. Means of CFU/ml of the five groups were compared for statistical differences, by analysis of variance (ANOVA).

Five groups, each of 5 randomly selected chicks, infected with Ampicillin-resistant *E. coli* were used for a trial. Two days before the trial, 2 groups were placed on poultry feed, fortified with additional 375 mg of Vitamin A, 10 mg of Vitamin C, 75 mg of Vitamin E and 12.50 mg of Selenium for each 25 kg bag. Three groups were left on ordinary poultry feed. The 2 groups on the fortified feed were treated with Ampicillin and with the Ampicillin-MSAMS® drug formulation respectively, at dose of 7.5 mg/kg for 7 days. Two of the groups on ordinary feed were treated at dosage of 10 mg/kg with 100% Ampicillin and with the Ampicillin-MSAMS® drug formulation respectively, for seven days while the third group on ordinary feed served as control. Means of *E. coli* CFU/*m*l of bile of the groups of chicks were compared for statistical differences, by ANOVA.

Five groups of randomly selected mice, infected with *Helignosomoides bakeri* were used for another trial. Two groups each were treated with piperazine and with piperazine-MSAMS® formulation at piperazine`s dosages of 110 mg/kg and 82.5 mg/kg, respectively. The fifth group served as control. *H. bakeri* Eggs Per Gramm (EPG) of feces of each mouse in the five groups were counted. Mean EPG of the groups were compared for statistical differences by ANOVA.

Fifteen Chloroquine resistant *Plasmodium berghei* infected albino mice were randomly assigned to five groups of three each and treated at two Chloroquine dosage levels (7 mg/kg and 5.25 mg/kg). Three groups were treated at Chloroquine`s dosage of 7 mg/kg with: Chloroquine, Chloroquine-MSAMS® formulation and Chlo-

roquine-MSAMS® formulation plus B-vitamins, respectively. The fourth group was treated at 75% of Chloroquine-dosage (5.25 mg/kg) with the Chloroquine-MSAMS® formulation plus B-vitamins while the fifth group was not treated (control). To ensure safety for the mice and uniformity for the experiment, the two Chloroquine formulations were reconstituted, such that each mouse was drenched same volume (0.1 ml) to deliver the two different dosages (7 mg/kg or 5.25 mg/kg) from the two different formulations (Chloroquine and Chloroquine-MSAMS®). For each of the treated groups, treatment was initiated 10 days post infection and lasted for 7 days. *Plamodium berghei* parasitaemia was tested for, on days: 1, 7, 14 and 21 post treatment and their means were compared for statistical differences.

Two groups of randomly selected chicks, infected with Sulfadimidine-resistant *E. coli* were treated at Sulfadimidine's dosage of 1 g/liter of drinking water with a 100% Sulfadimidine powder and with the Sulfadimidine-MSAMS® formulation, respectively. Two other groups were treated with the 100% Sulfadimidine and with the Sulfadimidine-MSAMS® drug formulation at Sulfadimidine's dosage of 0.75 g/liter. The fifth group served as control. After 5 days of treatment, dilutions of bile from the chicks were plated on Mc-Conkey agar and incubated at 37˚C for 24 hours. *E. coli* colonies in each culture were counted and expressed as CFU/ml. Means of *E. coli* CFU/ml of bile of the different treatment-groups were compared for statistical differences by ANOVA.

Results

- Recommended dosage of Ampicillin (10 mg/kg) led to 80.68% reduction of *S. gallinarum* per ml of bile of infected chicks. When MSAMS® was formulated to Ampicillin at that dosage, the infections-reduction improved ($P \leq 0.05$) to 86.36%. Reducing the dose to 75% of the recommended dosage (7.5 mg/kg) with the Ampicillin-MSAMS® formulation improved the rate of reduction ($P \leq 0.05$) to 97.84% (termination).
- Recommended dosage of Ampicillin (10 mg/kg) led to reduction of load of Ampicillin-resistant *E. coli* in bile of infected chicks by 50% (no cure). When MSAMS® was formulated to Ampicillin, rate of the resistant infection-reduction decreased ($P \leq 0.05$) to 43.91%. Use of 75% of the recommended dosage (7.5 mg/kg) of Ampicillin to which MSAMS® was formulated plus antioxidants (in feed of the chicks) for the treatment, led to 95.70% reduction of load of the resistant infection (infection-termination).
- Recommended dosage of Piperazine (110 mg/kg) led to 82.94% reduction of *H. bakeri* burden in mice. When MSAMS® was formulated to Piperazine, the rate of reduction improved ($P \leq 0.05$) to 92.04%. Reducing the dose to 75% of Piparazine`s recommended dosage (82.5 mg/kg) and formulating MSAMS® to it improved rate of reduction of the EPG ($P \leq 0.05$) to 96.82% (termination of the worm infestation).
- Mean parasitemia, 42.00 ± 15.74 in a group of mice infected with Chloroquine resistant *P. berghie* and treated with recommended dosage of Chloroquine (7 mg/kg) did not vary ($P > 0.05$) from 52.50 ± 11.99, 37.22 ± 11.88 and 33.57 ± 12.62 of the untreated group, the group treated with 7 mg/kg (Chloroquine-MSAMS®) and the group treated with 7 mg/kg (Chloroquine-MSAMS®) plus B-vitamins respectively but mean parasitemia, 00.00 ± 00.00 of the group treated with 75% of recommended dosage of Chloroquine (5.25 mg/kg) to which MSAMS® was formulated plus B-vitamins was significantly ($P \leq 0.01$) lower than parasitaemia of both the untreated group and of the other treated groups (termination of the infection).
- Recommended dosage of Sulfadimidine (1 g/liter of drinking water) led to increase ($P \leq 0.05$) of load of Sulfadimidine-resistant *E. coli* in bile of infected chicks by 259%. When MSAMS® was formulated to the medicine at that dosage, load of the resistant infection increased further ($P \leq 0.05$) by 789.10%. Reducing Sulfadimidine`s dosage to its 75% (0.75 g/liter) and formulating MSAMS® to it reduced load of the resistant infection by 84.34% (cure of resistant infection).

Discussion

In addition to mortalities and sicknesses which result from AMR, it is of economic importance because of low livestock productivity it causes and drug-patents it renders useless [1]. Recent suggestions that use of antimicrobials in livestock production should be discouraged in order to reduce drug residues in meat, eggs, milk and other human foods of animal origin as a preventive measure to slow rate of spread of AMR may cause even more damage to economy of some nations because banning use of antimicrobials in poultry and livestock could reduce their productivity. Efforts to develop new antimicrobials to replace those that have become useless due to AMR are expensive and time-consuming. It is better to adopt formulating approved pharmaceuticals to antimicrobials to improve their efficacies in order to prevent development of resistance against them and to help those that pathogens have already overcome, regain their efficacies.

Aluminum magnesium silicate (AMS) is an approved medicine and pharmaceutical stabilizing agent. As a stabilizing agent, it prolongs time medicines remain at high bioavailability and since its molecules consist of nanoparticles (0.96 nm thick) [4] it also enhances delivery of medicines to effect-targets. Both prolonging time of high bioavailability and enhancing delivery to effect-targets improve efficacy. Improving efficacy of antimicrobials reduces their doses required to achieve desired effects. Using lower doses for desired effects reduces side effects of medicines so that immune responses of patients improve. With enhanced efficacy of antimicrobials and improved immunity of patients, the ≥ 95% infection-reduction needed to achieve termination of infections [2] is possible. If treated infections are terminated, none will be left that could become resistant to antimicrobials used for the treatment. Improving antimicrobials` efficacies and enhancing patients` immunity would also lead to antimicrobials regaining efficacies against already resistant infections as observed with Ampicillin against *E. coli*, Sulfadimidine against *E. coli* and Chloroquine against *P. berghei* in these trials. Using lower doses to achieve desired effects will also reduce amount of antimicrobial residues in meat, milk, eggs, fish, honey and other human foods of animal origin. Reducing residues of antimicrobials in human foods will help in preventing new cases of AMR.

Apart from benefits to human health and animal health, using MSAMS® and other approved pharmaceutical nano-stabilizing agents to overcome resistance will improve economy of nations. Productivity of livestock will improve, patents to which AMR has been developed will come back to market and those not yet affected will be saved from the problem. Pharmaceutical industries will spend less in producing drug-formulations since drug-dosages will generally reduce.

Since the strategy of formulating MSAMS® (the nano-stabilizer) to medicines has been effective on Ampicillin (antibiotic), Piperazine (anthelminthic), Sulfadimidine (antibacterial/antiprotozoal) and Chloroquine (antimalarial), formulating nano-stabilizers to medicines may be a general solution for AMR. MSAMS® may be effective in enhancing efficacies of other classes of medicines to reduce their doses needed for effects. This will reduce cost of treatments both in humans and in Veterinary practice.

Limitations to using AMS for improvement of efficacies of medicines include that: some countries do not have the solid mineral as a natural resource; it is not mixable with some medicines; its route of administration is only oral; it is not absorbable. In these trials, two other medicinal solid minerals, Aluminum silicate and Magnesium silicate were reacted to get an AMS-brand patented as MSAMS® and it worked very well while Dextrose monohydrate successfully conveyed the formulations into blood for them to act systemically. For the problem of not being mixable with some medicines, studying time it takes MSAMS®, taken orally, to come into blood and time each medicine of interest becomes available in the blood, following treatment by its route of administration could determine when MSAMS® and the other medicines can be administered to achieve *in vivo* stabilization. That strategy will prevent AMR, cure already resistant infections, reduce doses of medicines for treatments, reduce costs of treatment and reduce side effects of medicines.

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