Original Article

Therapeutic use of sulfadimethoxine-ormetoprim for control of *Streptococcus agalactiae* infection in Nile tilapia (*Oreochromis niloticus*) fry

Nion Vinarukwong[1] Mintra Lukkana[2] Jan O. Berntsen[3] Janenuj Wongtavatchai[1*]

Abstract

The therapeutic efficacy of sulfadimethoxine-ormetoprim (SDMX-OMP) against *Streptococcus agalactiae* (*S. agalactiae*) infection in tilapia (*Oreochromis niloticus*) was examined in tilapia fry. Fish (3±0.44 g) underwent 3-hour immersion challenge with 50% infective dose (2.58 x 10^6 CFU/ml) of *S. agalactiae* and were treated at 24 hours post challenge with daily dosages of 30 and 50 mg SDMX-OMP/kg body weight (BW) feeding medication for 7 days. The administration of medicated feed increased the survival of the infected tilapia fry. The survival rate of the challenged, non-medicated group was 51.25±4.79%. The fish which were challenged with *S. agalactiae* and received the 30 and 50 mg treatment showed significantly improved survival rate at 82.50±2.89% and 92.50±2.89%, respectively. Streptococcal bacteria were not recovered from the challenged survivors treated with SDMX-OMP (n=140) while the non-treated survivors showed *S. agalactiae* isolation 8 out of 41 fish (19.51%). The substantial increase in the number of proper survivors following the medication suggests that SDMX-OMP given at 50 mg/kg BW for 7 days could effectively control streptococcal infection in tilapia fry. The application of this study is particularly important for fish hatchery to control streptococcal infections affecting fish fry when they are premature for vaccination.

Keywords: Nile tilapia fry, streptococcal infection, sulfadimethoxine-ormetoprim

[1]*Department of Medicine, Faculty of Veterinary Science, Chulalongkorn University, Bangkok 10330, Thailand*
[2]*National Bureau of Agricultural Commodity and Food Standards, Ministry of Agriculture and Cooperatives, Bangkok 10900, Thailand*
[3]*PHARMAQ AS, Harbitzalléen 5, P.O.B. 267 Skøyen, N-0213 Oslo, Norway*
***Correspondence**: janenuj.w@chula.ac.th*

Introduction

Nile tilapia (*Oreochromis niloticus*) is a freshwater culture species which has gained in popularity in many countries as supplies for global food demand (Fitzsimmons, 2016). However, massive production leads to intensive farming practices which result in the raising of stocking densities, poor aeration and water quality. These unfavorable conditions induce stress and, consequently, increase susceptibility to diseases or infections (El-Sayed, 2006). Streptococcosis is now considered to be a frequent disease of farmed tilapia in different areas of the world such as Asia (China, Japan, Singapore, Taiwan and Thailand), the Middle East (Bahrain and Israel), North America (Canada, Mexico, the United States, and the Caribbean), and South America (Brazil) (Agnew and Barnes, 2007; Amal and Zamri-Saad, 2011; Ortega et al., 2018). *Streptococcus iniae* and *Streptococcus agalactiae* are two significant species that cause high mortality (up to 50-75%) and severe economic loss in tilapia aquaculture (Al-Harbi, 2016). According to previous studies, *S. agalactiae* is a prime etiological agent of streptococcosis in tilapia farming in Thailand (Wongtavatchai and Maisak, 2008; Suanyuk et al., 2010; Jantrakajorn et al., 2014).

Antimicrobial and chemotherapeutic agents have been used to control bacterial infections in fish farming. In the United States, only three antimicrobial drugs are authorized for bacterial treatment in food fish (i.e. oxytetracycline, florfenicol and sulfadimethoxine-ormetoprim) and applications of these compounds are limited to control mortality from specific disease associated with specific pathogens (21CFR558.575) (Benbrook, 2002; USFDA, 2018). In addition to the 3 antimicrobial compounds, the Food and Drug Administration of Thailand (FDA) allows amoxicillin and enrofloxacin for the use in bacterial treatment in farmed fish (Wongtavatchai, 2017). Sulfadimethoxine-Ormetoprim (SDMX-OMP; Romet®30, PHARMAQ, Norway) has been approved for treatment of bacterial infections in aquaculture in many countries such as Canada, Colombia, Panama, the Philippines, Thailand, the United States and Vietnam. Romet®30 is one of the few antimicrobials explicitly approved for therapeutic use in aquaculture (Kawano et al., 2012; USFDA, 2018). It contains 25% sulfadimethoxine and 5% ormetoprim and possesses bacteriostatic activities with the inhibition of bacterial protein synthesis at steps of folic acid metabolism. The therapeutic dosage of Romet®30 is 50 mg of active ingredient per kg fish per day for 5 consecutive days. The withdrawal period is 3 days in catfish and 42 days in salmonids before slaughter or release as stocker fish (PHARMAQ AS, Oslo, Norway). Previous studies reported that Romet®30 was effective in controlling *S. iniae* experimental infection in tilapia (Clark et al., 2000), *Edwardsiella ictaluri* infection in channel catfish (*Ictalurus punctatus*) (Johnson and Smith, 1994; Wise and Johnson, 1998) and ciliated *Cryptocaryon irritans* infection in red sea bream (*Pagrus major*) and tiger puffer (*Takifugu rubripes*) (Kawano et al., 2012).

Because an effective control of streptococcosis at the early stage of tilapia fry is an extensive relevance to prevent disease outbreaks, the present study conducted feeding medication trials to examine the efficacy of SDMX-OMP for treatment of experimentally induced streptococcosis in tilapia fry. Effective feeding medication is an imperative mean to control streptococcus in tilapia hatchery because disease prevention with vaccination or other treatments could be inefficient at that stage.

Materials and Methods

Animal: Tilapia weighing approximately 3±0.44 g were purchased from a good agricultural practice approved hatchery and stocked in the facility at the Faculty of Veterinary Science, Chulalongkorn University. Animal management was approved by the ethics committee of Chulalongkorn University Animal Care and Use Committee (CU-ACUC; Approval No. 12310086). Three hundred and thirty six tilapia fry were placed in a flow-through system and the stocking density was 336 fish/500 L tank. Water quality during the study was maintained as dissolved oxygen (5.5-6.5 mg/l), pH (7.0-7.5), ammonia (<0.1 mg/l), alkalinity (100 mg/l) and water temperature (28-32°C). Sixteen fish of the stocked fish (5% of stocked fish) were randomly sampled for a pre-study health examination (PSHE) to determine their suitability for the trial. A batch showing ectoparasitic infestation or bacterial infection was excluded from the study. Fish passing the PSHE were acclimated in experimental aquaria for 7 days prior to the trial to ensure that there were no adverse effects due to acclimation stress. The fish were fed commercial dry pellet twice a day approximately 7% of their body weight (BW) and starved for 24 hours prior to the bacterial challenge until 24 hours post challenge.

Bacterial culture: *S. agalactiae* was isolated from the diseased tilapia fry in Phetchaburi province. The clinical isolate was grown on Tryptone Soya Agar (TSA; OXOID®, UK) containing 5% sheep blood at 30°C for 18-24 hours. The bacteria were propagated in Tryptone Soya Broth (TSB; OXOID®, UK) in a shaking incubator (SI4, Shel Lab, Cornelius, OR, USA) at 30°C, 100 *rpm* for 14 hours. The bacteria were harvested by centrifugation 3,500 g (Sigma 4-16 PK, Sartorius AG, Gottingen, Germany) at 4°C for 20 minutes and resuspended in sterile normal saline for the challenge experiment. Bacterial concentration was counted using a serial 10-fold dilution technique and the actual number of CFU/ml on blood agar was recorded.

Determination of infective dose: A preliminary immersion bath challenge experiment was conducted to determine the 50% infective dose (ID_{50}) of the bacterial strains. A hundred fish were randomly divided into 5 groups, each of 20 fish (10 fish x 2 replicates). Ten fish per group were randomly allocated from the holding tank to aquaria containing 20 L of running water with full aeration. These groups were immersed for 3 hours in static, aerated aquaria at different doses of *S. agalactiae*; 1.38×10^2, 1.38×10^4, 1.38×10^6 and 1.38×10^8 CFU/ml; and one non-challenged, negative control group. The fish were removed from the aquaria for each exposure test and returned to the aquaria after the immersion of *S. agalactiae*. Results

were evaluated clinically for 7 days post challenge. Moribund or dead fish were recorded and removed from the tanks for bacterial isolation and identification. *S. agalactiae* infection was confirmed in all diseased fish by bacterial isolation and PCR (Martinez et al., 2001). The number of fish found to be clinically infected or dead because of the challenge was analyzed using Probit analysis (SPSS Statistics 17.0, SPSS Inc., USA) to estimate infective dose values. The challenge doses at ID_{50} was used for the challenge experiment in further studies.

Preparation of medicated diet: Romet®30 [SDMX-OMP, 25/5 (w/w)] (PHARMAQ, Norway) was suspended in fish oil to prepare a liquid slurry for moistening commercial fish pellets (Grobest8901, GROBEST Co., Ltd, Thailand) for provision of a daily dosage of 100 or 170 mg/kg of fish BW, equivalent to SDMX-OMP active ingredient of 30 or 50 mg/kg BW for fish fed 7% of their BW per day. These dosages corresponded to the manufacturer's instructions. The medicated pellets were air dried for 24 hours and then frozen at -20°C until use.

Challenge protocol: Three hundred and twenty fish (3±0.44 g) from the storage tank were randomly divided into 4 groups, each of 80 fish (20 fish x 4 replicates). Twenty fish per group were randomly allocated from the holding tank to aquaria containing 20 L of running water with full aeration. Three challenged groups were moved to a new tank and immersed with static aerated water containing 50% infective dose of *S. agalactiae* suspension for 3 hours, then returned to their aquarium. The non-challenged, negative control group was also moved to a new tank and immersed with static aerated water for 3 hours, and then moved to their aquarium. Feeding medication was started 24 hours after the bacterial challenge and continued daily for 7 days. The challenged groups were treated with medicated feed (30 or 50 mg SDMX-OMP/kg BW) while the non-medicated groups were fed a similar basal diet (7% of fish BW/day). The feeding ratio was adjusted based on the fish feed intake, but the daily dosage of 30 or 50 mg SDMX-OMP/kg BW was maintained throughout the 7-day trial.

Interpretation of results: The fish were observed for 21 days post challenge. Moribund or dead fish were recorded and removed from the tanks for bacterial isolation and identification with an API 20 system to confirm the cause of death. Survival rates were evaluated at 14 days after treatment with SDMX-OMP at 30 and 50 mg/kg BW/day for 7 days. At the end of experiment, all survivors were tested for bacteriology and post-treatment health evaluation. The treatments were compared on the basis of cumulative mortality and body weight of survivors at the end of the study using a non-parametric test and one-way analysis of variance. Treatment effects were considered significant at P=0.05.

Results

The infective dose determination was conducted in a static bath exposure of *S. agalactiae* suspension at 1.38 x 10^2-1.38 x 10^8 CFU/ml for 3 hours, thereafter the fish were observed for clinical infection and mortality for 7 days post challenge. Fish with clinical signs of streptococcal infection; darkening, lethargy, erratic swimming; and dead fish observed during the experiment were confirmed to have *S. agalactiae* infection by PCR. The cumulative numbers of infected fish were analyzed for ID determination using Probit analysis. Fig. 1 demonstrates the correlation of bacteria concentrations with numbers of the infected fish observed within 7 days following 3-hour immersion of *S. agalactiae* clinical isolate. The correlation provided values of ID_{50} 2.58 x 10^6 CFU/ml.

Mortality in the challenged fish was observed after challenge to 16 days post challenge (Fig. 2). Diseased fish showing darkening, lethargic and neurological signs of erratic swimming were observed in the later stages of the infection (i.e. 5 days post challenge). The gross lesions revealed petechial skin hemorrhage, hemorrhage at base of fins and operculum, and abdominal distension. The internal lesions exhibited serosanguinous fluid in the body cavity, pale liver and splenomegaly. The groups receiving SDMX-OMP medicated feed had acceptable feed consumption while the challenged, non-medicated fish (positive controls) exhibited decreasing feed intake on the second day post challenge.

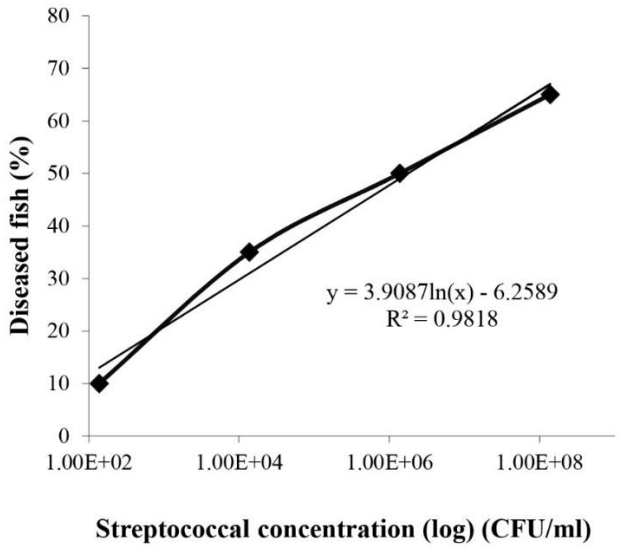

Figure 1 The correlation of bacterium concentration (CFU/ml) and infectivity (%) observed in tilapia fry for 7 days, following 3-hour immersion of *S. agalactiae* clinical isolate at different concentrations (ID_{50} was 2.58 x 10^6 CFU/ml)

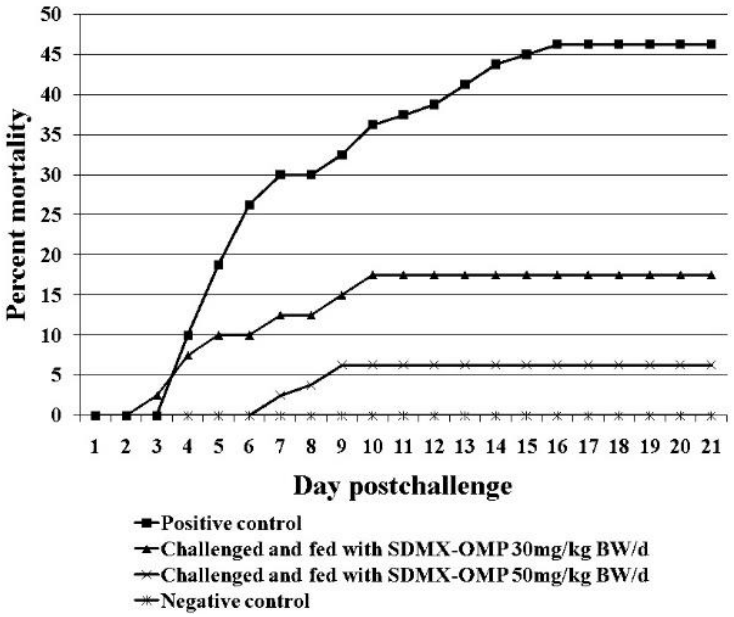

Figure 2 Cumulative percentage mortality of tilapia immersion challenged with *S. agalactiae* and then fed SDMX-OMP at daily rates of 30 and 50 mg/kg body weight for 7 days. Non-challenged fish fed on a basal diet were negative controls. Challenged fish fed on a non-medicated basal diet were positive controls. Each treatment group had 80 fish equally divided among four aquaria.

The survival rate evaluated 21 days post challenge (or 14 days after 7-day medication) of the challenged, non-medicated group was 51.25±4.79% while that of the negative control group (non-challenged, non-medicated) was 96.25±2.50%. The fish which were challenged with 2.58 x 10^6 CFU/ml of *S. agalactiae* and received daily dosages of 30 and 50 mg/kg BW for 7 days showed significantly improved survival rate at 82.50±2.89% and 92.50±2.89%, respectively. Significantly better survival rates of all treatment groups compared to the challenged, non-medicated positive control group was observed (Table 1). At the end of experiment, the challenged fish which received SDMX-OMP medicated feed were negative of *S. agalactiae* isolation (140 survivors) while the positive control group revealed *S. agalactiae* isolation in 8 out of 41 survivors.

Table 1 Percent survival (mean ± SD) of tilapia fry at 21 days post challenge with *S. agalactiae* clinical isolate and fed different daily dosages of SDMX-OMP medicated feed for 7 days

Challenged			Non-challenged**
SDMX-OMP (mg/kg BW)			
0*	30	50	
51.25±4.79[a]	82.50±2.89[b]	92.50±2.89[b]	96.25±2.50[c]

* Positive control; challenged/non-medicated fish
** Negative control; non-challenged/non-medicated fish
Means followed by different superscript letters are significantly different (P<0.05).

The body weights of tilapia fry were not significantly different between treatments at the beginning of the efficacy trial. The mean body weight of each experimental group was determined at 21 days post challenge. The body weights of the challenged groups receiving SDMX-OMP medicated feed at 30 and 50 mg/kg BW for 7 days were 9.53±0.30 g and 9.66±0.20 g, respectively, significantly higher than the body weight of the positive control group (6.03±0.14 g). The challenged, medicated fish gained weight, similar to the non-challenged, negative control group, whereas the non-medicated, challenged-survivals lost weight (Fig. 3).

Discussion

The use of antibacterial compounds in aquaculture for disease control is needed in early stage fry before vaccination can be implemented. This study clearly demonstrates that the oral administration of SDMX-OMP medicated feed at levels of 30 and 50 mg/kg BW per day for 7 consecutive days increases the survival of tilapia fry experimentally infected with *S. agalactiae*. Our study successfully induced streptococcoal infection in tilapia fry without injury to the fish skin, although the abrading skin method is a usual practice to induce streptococcal infection in tilapia (Darwish et al., 2002; Darwish and Hobbs, 2005; Bowker et al., 2010; Darwish, 2010). The fish receiving no treatment died 4 days post challenge and the cumulative mortality gradually increased until 16 days. The fish infected with *S. agalactiae* and subsequently treated with SDMX-OMP medicated feed showed delimited cumulative mortality.

The efficacy of higher SDMX-OMP dose is distinguishable in the survival of challenge experiment, 92.5±2.8% in the 50 mg treatment compared to 82.5±2.8% in the 30 mg treatment, suggesting that the efficacy of 50 mg treatment is more competent than the 30 mg treatment. The negative streptococcal bacteria isolation in the medicated survivors at the completion of the experiment indicates effective inhibition of the

pathogen by the medication. Concentrations of SDMX-OMP in tilapia tissues at 1 hour following oral administration of 50 mg SDMX-OMP/kg BW/day for 5 days were 2.75/0.36 µg/g in muscle skin and 10.40/0.36 µg/ml in serum (Kosoff et al., 2007). The significant increase in survivals of the challenged, medicated tilapia may support the serum SDMX-OMP level exceeding the minimum inhibitory concentration (MIC) of the compound against the pathogen.

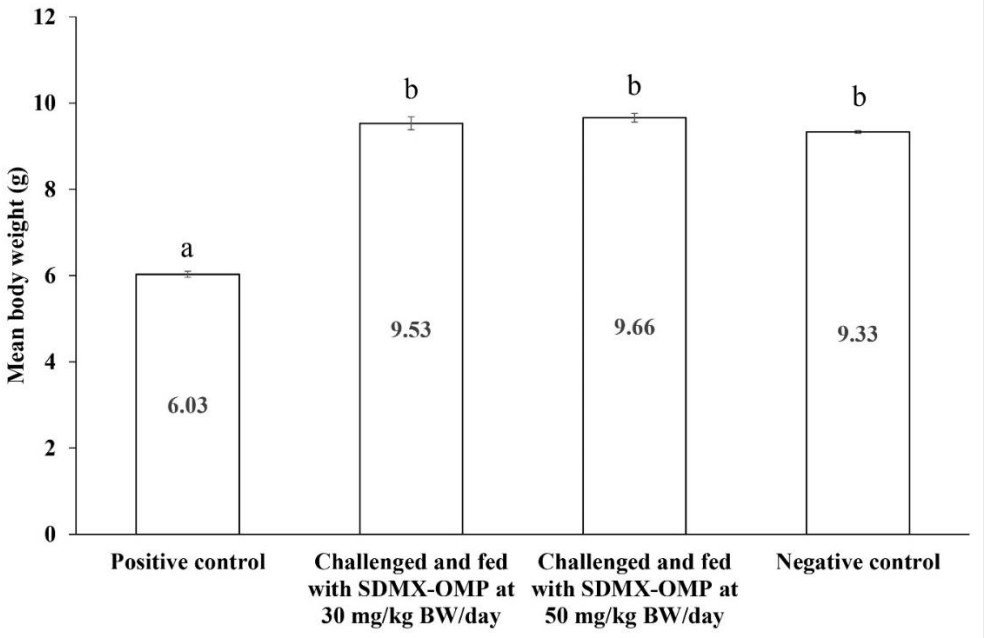

Figure 3 Body weight (g) of survival tilapia fry measured at the completion of 21-day trial period. Fish were challenged with 2.58 x 10^6 CFU/ml for 3 hours, followed by feeding medication providing daily dosages of SDMX-OMP of 30 or 50 mg/kg BW for 7 days. Non-challenged fish fed on a basal diet were negative controls. Challenged fish fed on a non-medicated basal diet were positive controls. Fish were observed for 14 days after the 7-day treatment course. Different superscript letters are significantly different (P<0.05).

The effect of chemotherapeutic agents administered to fish leading to lower body weight gain is generally attributed to reduced feed intake of the diseased fish and poor palatability of the compound (Gaikowski et al., 2013). Feeding inappetence of the diseased fish makes disease control with feeding medication unsuccessful; therefore, disease detection at an early stage of infection is critical to make oral therapy effective (Darwish and Hobbs, 2005; Matthews et al., 2013). In the present study, the feeding medication was introduced 24 hours post challenge while the feeding activity of the fish was still unaffected by the infection. The SDMX-OMP medicated feed prepared by suspension of SDMX-OMP in fish oil and subsequently used as liquid slurry to moisten the commercial fish pellet was well accepted by the fish. The increased BW of the challenged medicated fish was comparable to the non-challenged negative controls receiving regular (non-medicated) feed, indicating the efficacy of SDMX-OMP in controlling streptococcosis in tilapia fry without growth suppression. However, growth suppression associated with oral administration of SDMX-OMP was reported in healthy channel catfish fingerlings receiving SDMX-OMP medicated feed at 50 mg/kg BW daily for 11 weeks (Rábago-Castro et al., 2006). A previous study also showed that SDMX-OMP medicated feed at 40.5 mg/kg feed, fed at 2% BW for 5 consecutive days was ineffective in controlling infection of *E. ictaluri* in channel catfish fingerlings and that prolonged consumption of this feed might suppress antibody production in channel catfish (Wise and Johnson, 1998). The bitter taste of SDMX has also been reported to be a problem in trout, but suspension in gelatin slurry can overcome this problem. It is also important to begin the treatment while the fish still have a reasonable appetite (Darwish et al., 2002; Gaikowski et al., 2013).

The clinical outcome of this study shows that the use of feed containing SDMX-OMP at 30 and 50 mg/kg BW daily for 7 consecutive days successfully controls experimental *S. agalactiae* infection in tilapia fry. Significantly better survival and BW gain were found with the 50 mg SDMX-OMP-treated groups. The regular BW gain and negative bacterial isolation in the survivors at both doses demonstrates the effectiveness of SDMX-OMP in treating *S. agalactiae* infection in tilapia. The medication is particularly important for disease control in fish fry during their early development or prior to immunization. However, the discrepancy between our study and previous findings in channel catfish suggests that additional field studies are required to establish a recommendation for therapeutic use of SDMX-OMP at different stages of tilapia production.

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บทคัดย่อ

การใช้ยาต้านจุลชีพซัลฟาไดเมททอกซีน-ออร์เมทโธพริมขนาดรักษาโรค เพื่อควบคุมการติดเชื้อสเตรปโตคอคคัสอะกาแลคเทียในลูกปลานิล

นิอร วินารักษ์วงศ์[1] มินตรา ลักขณา[2] แจน โอเบิรนท์เซน[3] เจนนุช ว่องธวัชชัย[1*]

ทดสอบการใช้ยาต้านจุลชีพซัลฟาไดเมททอกซีน-ออร์เมทโธพริม (sulfadimethoxine-ormetoprim, SDMX-OMP) รักษาลูกปลานิล (3±0.44 กรัม) ที่ติดเชื้อ *Streptococcus agalactiae* (*S. agalactiae*) ด้วยวิธีการแช่เชื้อ *S. agalactiae* ขนาดที่ทำให้ลูกปลาติดเชื้อ 50% (Infective dose 50) คือ 2.58 x 10^6 CFU ต่อมิลลิลิตร เป็นเวลา 3 ชั่วโมง แล้วทำการรักษาด้วยการให้ยา SDMX-OMP *ผสมอาหาร* ขนาด 30 และ 50 มิลลิกรัมต่อน้ำหนักตัว 1 กิโลกรัม ติดต่อกัน 7 วัน พบว่าการให้ยาผสมอาหารเพิ่มอัตรารอดในลูกปลานิลที่ติดเชื้อ โดยอัตรารอดในปลากลุ่มควบคุมที่ได้รับเชื้อแต่ไม่ได้รับยาเท่ากับ 51.25±4.79% ส่วนปลาที่ได้รับเชื้อและได้รับยาขนาด 30 และ 50 มิลลิกรัมมีอัตรารอด 82.50±2.89% และ 92.50±2.89% ตามลำดับ เมื่อสิ้นสุดการทดลอง ไม่สามารถแยกเชื้อ *S. agalactiae* จากปลาที่ได้รับยา (n=140) แต่ตรวจพบเชื้อ *S. agalactiae* จากปลาที่รอดชีวิตโดยไม่ได้รับยาจำนวน 8 จาก 41 ตัว (19.51%) การให้ยา SDMX-OMP ขนาด 50 มิลลิกรัมต่อน้ำหนักตัว 1 กิโลกรัม เป็นระยะเวลา 7 วัน มีประสิทธิภาพในการควบคุมโรคติดเชื้อสเตรปโตคอคคัสในลูกปลานิลและเป็นวิธีที่ปฏิบัติในลูกปลาขนาดเล็กซึ่งยังไม่สามารถรับวัคซีน

คำสำคัญ: ลูกปลานิล การติดเชื้อสเตรปโตคอคคัส *ซัลฟาไดเมททอกซีน-ออร์เมทโธพริม*

[1]ภาควิชาอายุรศาสตร์ คณะสัตวแพทยศาสตร์ จุฬาลงกรณ์มหาวิทยาลัย กรุงเทพฯ 10330

[2]สำนักงานมาตรฐานสินค้าเกษตรและอาหารแห่งชาติ กระทรวงเกษตรและสหกรณ์ กรุงเทพฯ 10900

[3]PHARMAQ AS, Harbitzalléen 5, P.O.B. 267 Skøyen, N-0213 Oslo, Norway

****ผู้รับผิดชอบบทความ** E-mail: janenuj.w@chula.ac.th*