Comparison of caproic acid and monolaurin with zinc oxide and benzoic acid; effect on growth performance of weaned pigs

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Abstract

Medium chain organic acids (MCOA) offer the potential to replace zinc oxide, without dependence on antibiotic use, and can replace or reduce the use of benzoic acid in pig production. A study was conducted to evaluate the effects of caproic acid (C6) and C12 monolaurin (C12M) on the growth performance of weaned pigs, in comparison with zinc oxide (ZnO) and benzoic acid (BA). Specifically, the trial examined whether MCOA, at a reduced inclusion level of BA, could maintain performance levels of pigs similar to those receiving a higher inclusion level of BA. In total, 240 pigs from weaning until 27 d post-weaning were used in a completely randomised block trial with six treatments and eight replicate pens per treatment. Treatments were: (1) control (CON), basal diet (BD); (2) BD+ZnO (ZnO); (3) BD+5,000 mg/kg BA (BA); (4) BD+2,500 mg/kg BA+2,000 mg/kg C12M+700 mg/kg C6 (BA_{low}/MCOA); (5) BD+2,000 mg/kg C12M+700 mg/kg C6 (MCOA); (6) BD+1000 mg/kg C12M+700 mg/kg C6 (MCOA_{low}). Feed and water were provided *ad libitum*. Pigs receiving BA or BA_{low}/MCOA had improved feed conversion ratio (FCR) during the period 0-14 days, compared with control pigs (1.02 vs 1.17, $P<0.05$; 1.06 vs 1.17; $P=0.084$, respectively). The FCR of pigs receiving BA_{low}/MCOA was similar to those receiving BA at the higher inclusion-level. Pigs showed good health throughout the study, as indicated by clinical and faecal scores. Replacement of ZnO was inconclusive and further studies with more challenging health conditions are required to conclude benefits.

Keywords: antibiotics, pigs, performance, replacement, organic acids

1. Introduction

It is well established that the use of antibiotics in pig production need to be reduced in order to slow the development of antimicrobial resistance which occurs through genetic mutation (vertical transmission) or acquiring resistance genes from another bacterium (horizontal transmission), including other species of bacteria (Munita and Arias, 2016). Antimicrobial resistance spreads throughout the environment as the bacteria move through, for example, sewage, waste and livestock products (Woolhouse *et al.*, 2015) and is present at unacceptably high levels in pig production systems (Holmer *et al.*, 2019; Pollock *et al.*, 2020; Zhang *et al.*, 2019). In the United Kingdom, the pig sector is still heavily dependent on prophylactic use both of antibiotics and zinc oxide (ZnO).

Despite voluntary reductions in recent years, antibiotics continue to be routinely administered to pigs as medicated feeds for a two-week period after weaning to prevent low-level infections.

Antibiotic use in 2019 was similar to levels reported in 2018, at 110 mg/population correction unit (PCU), having fallen 60% in the three years prior (AHDB, 2019). This figure indicates that 110 mg of antibiotic active ingredient was used for every kg of bodyweight at time of treatment. In the first half of 2020, antibiotic usage dropped to 104 mg/PCU; a significant achievement towards the 99 mg/PCU target set in 2017 (AHDB, 2020). However, new targets have now been established for a 30% reduction between 2020 and 2024 (RUMA, 2020). Regulation EU 2019/4, which comes into force in January 2022, will prohibit the prophylactic

use of antibiotics in the European Union, except for very exceptional cases and to treat individual animals.

In parallel, there is an urgency to remove ZnO from piglet starter feeds to meet legislation in place as a result of environmental and toxicity concerns, including microbial cross-resistance. The European Medicines Agency's Committee for Medicinal Products for Veterinary Use concluded that the overall benefit-risk balance for veterinary medicinal products containing ZnO was negative, as benefits for the prevention of diarrhoea in pigs did not outweigh the risks for the environment. They recommended withdrawal by 2022 of the existing marketing authorisations for veterinary medicinal products containing ZnO (European Commission, 2017). ZnO was estimated to be used in 70-90% of weaned pig rations in 2017 (NPA, 2017), although it is expected that this figure has since reduced in response to pending legislation. There are concerns that the removal of ZnO may lead to a rise in antibiotic dependence. Furthermore, the cost of endemic pig disease, estimated at around £190-250 million/annum in the UK (ProHealth FP7 consortium, 2015), could increase if antibiotics are withdrawn without viable alternatives. Benzoic acid is widely used to reduce and replace in-feed antibiotics and ZnO, but there may be concerns about long-term use of high levels in pig feeds.

There is an ongoing drive to develop alternatives to antibiotics and ZnO. Among the candidates of interest, medium chain organic acids (MCOA) have received attention interest due to their strong antimicrobial properties. These are monocarboxylic acids which are unbranched and unsaturated, and consist of caproic acid (C6:0, hexanoic acid), caprylic acid (C8:0, octanoic acid), capric acid (C10:0, decanoic acid) and lauric acid (C12:0, dodecanoic acid). Monoesters of free fatty acids may be formed; for example, monolaurin is a monoester formed from glycerol and lauric acid. The antimicrobial activity of MCOA has been extensively reviewed by Hanczakowska (2017). The undissociated acid molecules penetrate the phospholipid bilayer membrane of bacteria and enter the cell where they dissociate in the alkaline pH. The pH of the cell cytoplasm is lowered, suppressing cytoplasmic enzymes and nutrient transport systems, which leads to cell death. Several studies have shown stronger inhibitory effects with MCOA than with short or long chain organic acids (Hanczakowska *et al.*, 2013; Hassinen *et al.*, 1951; Nieman, 1954). There are conflicting reports about the relative antimicrobial efficacy of different MCOA. Only caprylic acid (C8:0), and, to a lesser extent, capric acid (C10:0) have shown significant antimicrobial activity against two strains of *Escherichia coli* in one study (Marounek *et al.*, 2003). However, in another study, both lauric acid (C12:0) and caprylic acid (C8:0) had the ability to damage the cytoplasmic structure of bacteria (Skrivanová *et al.*, 2006). Lauric acid was shown to disrupt *Clostridium* spp.

cell membranes and cytoplasm (Shilling *et al.*, 2013). Monolaurin was shown to be more active than the free fatty acids against gram positive bacteria (Batovska *et al.*, 2009). Other *in vitro* studies (Neath *et al.*, in press), confirmed the efficacy of monolaurin against Gram positive bacteria, *Staphylococcus aureus* and *Streptococcus suis*, whereas caproic acid had activity against gram negative bacteria, including *Salmonella typhimurium* and *E. coli*, as well as against gram positive bacteria. A combination of monolaurin (C12M) and caproic acid (C6:0) may therefore be beneficial to replace prophylactic ZnO, without resorting to antibiotic use, and partially replace benzoic acid (BA) without any reduction in pig performance.

To test this hypothesis, the following study was conducted to evaluate a blend of MCOA consisting of C12M and C6:0 on the growth performance of weaner/grower pig in comparison with standard ZnO or BA.

2. Materials and methods

Animals and trial design

The trial was carried out in accordance with the U.K. Animals (Scientific Procedures) Act, 1986 and associated guidelines. Two hundred and forty (Large White × Landrace) × Danish Duroc pigs selected for use in the trial were weaned at an initial weight 8.1 ± 1.41 kg (mean ± SD) at 26.0 ± 1.25 days of age. The experiment consisted of 48 pens, each containing five mixed sex pigs. Start weight, sex and litter of origin were balanced across treatments within replicates. Pens within each replicate were randomly assigned to one of the six dietary treatments shown in Table 1. Pens measured 2.8×2.0 m with plastic coated fully slatted flooring (without bedding) and nipple drinkers. Pigs remained on the trial for 27 days after weaning, with an average final BW of 19.82 ± 3.43 kg. Feed and water were provided *ad libitum* throughout the experimental period.

Dietary treatments

A two-phase feeding programme was used: phase 1 from weaning to d 14 and phase 2 from d 15 to d 27. Diets were provided by a UK commercial feed producer according to a commercial specification. Feed-grade BA, ZnO, caproic acid and monolaurin were obtained from commercial manufacturers. A standard level of BA inclusion (5,000 mg/kg), as used in previous studies, was reduced by 50% to determine whether a lower dose-rate could be mitigated by adding medium chain organic acids. The level of monolaurin was based on the commercially recommended level, reduced to 50% in the MCOA_{low} treatment. The level of caproic acid was reduced compared to the dose used in a previous trial, to determine whether a response could still be achieved, in combination with monolaurin. The level of ZnO used was the standard authorised dose-

Table 1. Dietary treatments.

Diet	Treatment ¹	0-14 d of trial	15-27 d of trial
1	Con	Basal diet	Basal diet
2	ZnO	ZnO (2,500 mg/kg zinc)	Basal diet
3	BA	BA 5,000 mg/kg	BA 5,000 mg/kg
4	BA _{low} /MCOA	BA 2,500 mg/kg; C12 M 2,000 mg/kg; C6:0 700 mg/kg	BA 2,500 mg/kg; C12 M 2,000 mg/kg; C6:0 700 mg/kg
5	MCOA	C12 M 2,000 mg/kg; C6:0 700 mg/kg	C12 M 2,000 mg/kg; C6:0 700 mg/kg
6	MCOA _{low}	C12 M 1000 mg/kg; C6:0 700 mg/kg	C12 M 1000 mg/kg; C6:0 700 mg/kg

¹ BA = benzoic acid; Con = control; MCOA = Medium chain organic acids; ZnO = zinc oxide.

rate (2,500 mg/kg in feed). The test additives were added by substitution of barley and pre-blended into 5.0 kg of wheat to facilitate uniform distribution, then pelleted through a commercial press using a 2 mm die. The nutrient specifications of the formulated diets are given in Table 2. Diets were colour coded, to allow the trial to be run under blinded conditions.

Measurements and analytical methods

Individual pig weights were recorded on days 0, 7, 14, 21, and 27. Feed troughs were emptied daily from weaning to d 21 and then at day 27 for the determination of pen feed intake. Average feed conversion ratio (FCR) per pen was calculated from body weight and feed intake measurements. Individual use of antibiotics, incidence of scours or other health problems and mortality were recorded. Faecal scores were evaluated by the same technician daily at the same time each day from Monday to Friday for the duration of

the trial, using the following scoring system: 1 = firm, 2 = soft, spreads slightly, 3 = very soft, spreads readily, 4 = watery, liquid consistency. Health scores were designated based on the proportion of pigs within a pen displaying signs of poor health with respect to mobility, demeanour or behavioural signs, and averaged over each feeding phase. For example, if a pen had 1 pig that seemed unwell it would score 0.2 (1/5).

Statistical analysis

Data were analysed according to a randomised complete block design using the general linear model function of SPSS (version 21; IBM Corp., Armonk, NY, USA) with pen designated as the experimental unit. Data were checked for normality of residuals using the Kolmogorov-Smirnov test and homogeneity of variance, using the Levene's test prior to analysis. Week 1 and diet 1 FCR data variance was heteroscedastic, and were subjected to a Kruskal-Wallis

Table 2. Basal diet specifications.

Ingredients (%)	0-14 d	15-27 d	Nutrients (% DM) formulated ¹	0-14 d	15-27 d
Barley	15.00	17.31	Crude protein	21.64	21.14
Oats	5.00	-	Oil A ²	7.30	4.27
Wheat	30.00	45.00	Oil B ³	7.98	4.94
Soya, extruded 48%	16.00	23.56	NDF	7.43	9.03
Soya, full fat	3.00	-	Ash	5.29	5.17
Fish meal 68%	5.00	4.00	Calcium	0.70	0.72
Dry skimmed milk	3.00	-	Phosphorus	0.70	0.65
Whey	14.44	4.65	SID phosphorus	0.44	0.38
Soya oil	5.00	2.70	Sodium	0.18	0.19
Limestone	0.20	0.57	SID lysine	1.37	1.23
Salt	0.82	0.74	SID methionine	0.53	0.44
Lysine HCl	0.35	0.31	SID threonine	0.89	0.80
Methionine	0.20	0.15			
Threonine	0.17	0.14	Nutrients (% DM analysed)		
Tryptophan	0.03	-	Crude protein	21.10	21.40
Monodical P	0.77	0.81	Oil A	7.44	4.49
L-Valine	0.05	-	Oil B	8.05	5.26
Phytase ⁴	0.04	0.04	NDF	7.31	8.1
Premix ⁵	0.50	0.50	Ash	5.40	5.2

¹ NDF = neutral detergent fibre; SID = standard ileal digestible.

² Oil A = crude fat; ether extractable portion; contains additional non-polar (ether soluble) components of diet.

³ Oil B = total fat; acid hydrolysis prior to ether extraction released any bound/ protected fats so that they can be extracted in the ether extract stage.

⁴ 6-phytase at 2,000 units/ kg feed.

⁵ Premix additives (per kg feed): vitamin A (3a672a retinyl acetate) 8,000 IU, vitamin D3 (3a671 cholecalciferol) 1,500 IU, vitamin E (all rac-alpha tocopherol acetate) (3a700) 125 IU, iodine (calcium iodate anhydrous 3b202) 1 mg, manganese (manganous oxide 3b502) 30 mg, copper (copper sulphate pentahydrate E4-copper) 80 mg, iron (iron sulphate monohydrate 3b103) 120 mg, selenium (sodium selenite E8-selenium) 0.25 mg, 1,220 U endo-1-4-beta-xylanase (EC 3.2.1.8), 152 U endo-1,3(4)-beta glucanase (EC3.2.1.6), 5 mg butylated hydroxytoluene (BHT E321).

test. Significantly different means were separated using the Tukey's post-hoc test. Data are presented as least-square means along with the pooled SEM. Significance was assigned at $P<0.05$ and $P>0.05$ and <0.1 were denoted trends. Faecal and health scores were analysed by Kruskal-Wallis using the non-parametric function of SPSS. Antibiotic usage was analysed by chi-square analysis. Incidence of death or pigs removed from the trial were not analysed statistically, due to insufficient observations. Data were analysed in terms of pen body weight at the start of the trial and weekly thereafter, feed intake (as average daily feed intake; ADFI) and daily liveweight gain (ADLG) calculated from measurements taken each week, weekly FCR, health and faecal scores.

3. Results

Growth performance and health results are presented in Table 3. Initial growth rates were slightly higher than average for this facility at 348 g/pig/d ($\pm$ SD 70.5) during the first three weeks post-weaning. This higher performance was maintained throughout the study, with pigs gaining an average of 432 g BW/d ($\pm$ SD 80.2) and consuming an average

of 510 g feed/pig/d ($\pm$ SD 92.1) over the 27 d experimental period. Over the course of the study, pigs consumed similar amounts of feed and grew at similar rates, irrespective of treatment, and overall FCR and body weights at the end of the study were comparable between treatments. Animals offered the BA or the BA_{low}/MCOA treatment performed similarly throughout the trial, and although not statistically significant from the other treatments, achieved the highest growth rates. Those receiving BA were, on average, 466 g heavier at the end of the study than those receiving feed without BA. Between 8-14 d, FCR for pigs receiving BA was better than the negative control diet (1.02 vs 1.17; $P<0.05$). The FCR for pigs receiving BA_{low}/MCOA was improved compared to the negative control diet between 0-14 d ($P=0.084$) and 8-14 d ($P<0.01$). In the period 0-14 d, the FCR of pigs receiving the MCOA or MCOA_{low} diets was not significantly different from the control diet. Improved FCR in the BA ($P<0.05$) and BA_{low}/MCOA ($P=0.084$) treatments was not seen in phase 2 or over the whole period.

Pigs were in good health generally with a low overall health score of 0.07 ($\pm$ SD 0.10), irrespective of dietary treatment, and there were no mortalities. The number of pigs removed

Table 3. Growth performance and health status of pigs fed medium chain organic acids in place of benzoic acid or zinc oxide.^{1,2}

Parameter	CON	ZnO	BA	BA _{low} /MCOA	MCOA	MCOA _{low}	S.E.M.	P-value
Weaning age	26.2	26.0	26.1	25.8	26.0	26.1	0.466	0.996
Liveweight (kg)								
d 0	8.17	8.13	8.12	8.15	8.21	8.08	0.528	1.000
d 7	9.18	9.14	8.98	9.25	9.35	9.09	0.103	0.201
d 14	11.39	11.49	11.73	11.84	11.66	11.53	0.213	0.702
d 21	15.13	15.33	15.90	15.79	15.36	15.19	0.317	0.417
d 27	19.73	19.55	20.11	20.16	19.77	19.63	0.423	0.874
LSM ADFI (g/d)								
d 0-7	191	184	167	195	200	187	10.7	0.348
d 8-14	345	338	356	355	349	334	14.1	0.846
d 15-21	656	640	689	681	633	640	22.2	0.359
d 22-27	947	866	935	936	889	929	31.1	0.406
0-14 d	268	261	261	273	274	260	11.1	0.877
15-27 d	790	744	903	799	751	773	23.9	0.390
Overall	517	494	519	524	504	502	15.6	0.722
LSM ADLG (g/d)								
d 0-7	145	144	123	158	162	144	14.8	0.514
d 8-14	313	337	386	361	329	339	19.3	0.145
d 15-21	534	547	595	565	529	511	24.5	0.221
d 22-27	766	704	702	728	735	740	36.1	0.815
0-14 d	230	240	256	262	246	245	15.0	0.731
15-27 d	641	620	645	640	624	617	21.8	0.901
Overall	428	423	443	444	428	427	15.5	0.884
LSM FCR								
0-7 d	1.22	1.17	1.17	1.18	1.18	1.18	0.027	0.857
8-14 d	1.13 ^b	1.01 ^{abc}	0.93 ^c	1.00 ^{ac}	1.06 ^{ab}	1.01 ^{abc}	0.028	<0.01
0-14 d ³	1.17 ^a	1.09 ^{ab}	1.02 ^b	1.06 ^{ab}	1.12 ^{ab}	1.08 ^{ab}	0.028	<0.05
15-27 d	1.26	1.21	1.24	1.25	1.21	1.26	0.031	0.755
Overall	1.22	1.17	1.17	1.18	1.18	1.18	0.026	0.755
Antibiotics ⁴	11	6	6	8	7	7		
Taken off trial (d)	1 (d 15)	0	1 (d 13)	1 (d 8)	0	1 (d 13)		
Reason	lame	-	poor health	abscess	-	poor health		

¹ ADFI = average daily feed intake; ADLG = average daily liveweight gain; BA = benzoic acid; Con = control; FCR = feed conversion ratio; LSM = least squares mean; MCOA = Medium chain organic acids; ZnO = zinc oxide.

² Means within row that do not share a common superscript letter differ significantly ($P<0.05$).

³ Con vs [BA_{low}/MCOA], $P=0.084$.

⁴ No. of pigs requiring antibiotic treatment; standard treatment of amoxycillin 15 mg/kg/day for 5 days.

from the trial was relatively low, at four. A total of 45 pigs (18.8%) required antibiotic treatment during the trial, with numbers equally distributed between the six treatments. Overall faecal consistency scores were uniformly good throughout the trial (mean = 2.11 ± 0.09 ; 'soft') with no differences observed between the treatments ($P=0.180$).

4. Discussion

The objective of this study was to test the concept of using MCOA in place of ZnO in pig weaner diets, either alone or as a partial replacement to BA. Benzoic acid, which is commonly used in commercial weaner diets in the UK, was used as a performance benchmark. There was a noticeable improvement in FCR in pigs receiving the BA treatment, and a lesser improvement for those receiving the BA_{low}/MCOA treatment. The performance improvements were visible from the growth and health measurements, which indicated there were no post-weaning health issues. In the second week of the study (d 8-14), only the BA-treated animals (BA and BA_{low}/MCOA) showed improvements in FCR, whereas those receiving ZnO showed no improvement in any growth performance parameters. The absence of any measurable effect of ZnO was likely due to the high health status of the animals in this study, as indicated by clinical health scores and faecal scores. Further studies should be conducted to assess the effects of the treatments under challenge conditions.

Animals offered the BA or the BA_{low}/MCOA treatments had the highest growth rates. Previous trials showed that ADLG increased by between 9 and 20% when BA was included at 5,000 mg/kg in feed (EFSA, 2005). However, such improvements were not seen in the current study, which may have been due to the relatively high growth rate. In previous studies (Portocarero, 2022) using a similar randomised block design, a blend of MCOA consisting of C6:0, C8:0, C10:0 and C12:0 was compared with ZnO and BA from weaning to 56 d post-weaning. Low initial growth rates were linked to high antibiotic usage and the removal of poorly performing pigs. Animals receiving BA plus MCOA or BA plus ZnO showed superior FCR and ADLG throughout the trial in comparison to the control diet. Dietary treatment influenced FCR throughout the study, with improvements reported for pigs fed BA plus MCOA compared to the control diet ($P=0.008$). A second study, carried out for 28 days post-weaning, compared a low and high inclusion level of MCOA plus ZnO and with a blend of either C6:0 and C12:0 or C6:0 and C12 monolaurin. An inclusion level of 1,500 mg/kg MCOA resulted in an improved FCR in pigs at three and four weeks after weaning ($P<0.05$), compared to the control diet. Pigs fed a blend of caproic acid plus monolaurin or caproic acid plus lauric acid showed similar FCR improvements to the pigs receiving blended C6:0, C8:0, C10:0, and C12:0.

The improvement in FCR seen in the BA_{low}/MCOA treatment group in the current study was encouraging as it confirmed that the dose rate of BA can be reduced and substituted with MCOA, without any reduction in performance. In grower-finisher diets, the recommended dose rate of 5,000 mg BA/kg feed was reduced (Regulation (EU) 2020/1031 of 15 July 2020), and the current results demonstrated that the lower level was still effective.

No improvements in ADLG due to MCOA were seen in this study. Other trials showed mixed results in response to MCOA. Hanczakowska *et al.* (2013) found that piglets receiving C8:0 caprylic acid, C10:0 capric acid, or a mixture of both from seven days of age had improved ADLG and FCR ($P<0.05$) by d 35 compared to the control group. ADLG was improved by 13-18.7% throughout the 84 d study. Gebhardt *et al.* (2020) reported linear increases in ADLG and ADFI ($P<0.01$) and FCR ($P=0.004$) when a 1:1:1 blend of C6:0, C8:0 and C10:0 was included at 1.5% in the diet. Thomas *et al.* (2020) found a linear increase in ADLG ($P<0.001$) when 2% of a blended C8:0/ C10:0 product was added to feed, and a linear increase in FCR at up to 1% inclusion. In contrast, only a 2.8% increase in ADLG was recorded with 2% MCOA in feed (Mohana Devi and Kim, 2014). Furthermore, Dahmer *et al.* (2020) found that a blend of C6:0, C8:0 and C10:0 did not significantly affect performance compared to a negative control diet, whereas ZnO (3,000 mg/kg) improved ADLG ($P<0.001$) but the inclusion level of MCOA was not specified. The size of response was likely influenced by the type and dose rate of MCOA and pathogen challenge. The current study demonstrated measurable improvements in feed conversion efficiency in response to a combination of BA, caproic acid and monolaurin, even when the background health and growth performance was good. However, effects of caproic acid and monolaurin in the absence of BA were inconclusive.

5. Conclusions

The addition of 5,000 mg/kg BA to an unmedicated weaner diet improved FCR. When the BA inclusion level was reduced to 2,500 mg/kg and the diet was further supplemented with monolaurin and caproic acid, FCR improvements were largely maintained. This suggested that medium chain organic acids including monolaurin and caproic acid may be used to partially replace BA in piglet diets and as part of a strategy to replace ZnO without resorting to antibiotic use.

Conflict of interest

The authors declare no conflict of interest.

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