Determination of the Magnitude and Duration of Penicillin Serum Levels in Swine Following a Single Intramuscular Injection of Procaine Penicillin G and of Benzathine Penicillin G

by

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INTRODUCTION

Penicillin is one of the most important antibiotics used in human and veterinary medicine. Although other antibiotics have become available since penicillin was developed, the penicillins are still a widely used, major antibiotic. New derivatives of the basic penicillin nucleus are being produced every year.[1] Little research has been done with the penicillins in swine since the initial studies in the 1950's.

There are several penicillin products available for the treatment of swine disease. Of these, the repository salt forms are the most commonly used. These are procaine penicillin G alone, and a form combining procaine penicillin G and benzathine penicillin G. Both of these repository salt forms have different properties. Procaine penicillin gives higher initial blood levels and then tapers off over a 24 hour period, while benzathine penicillin provides lower blood levels which are persistent over a longer span of time.

Because of these individual properties, the two forms have been combined in order to produce a drug which gives a moderately high blood level of penicillin initially, and a therapeutic blood level of penicillin for 48 hours.

In recent years, Streptococcus suis and Haemophilus pleuropneumonia have been diagnosed frequently in swine. Penicillin, based on sensitivity testing, is the drug of choice for both of these organisms. Many swine practitioners are prescribing the combination penicillin product in order to have penicillin blood levels for extended periods, however, there have been questions regarding the dosage of the

combination penicillin products. Many people have questioned if the dosage of penicillin should be based upon the total units of penicillin in the combination, or if it should be based upon the procaine penicillin G component. This study was conducted to determine the penicillin levels obtained in pigs with the two repository forms of penicillin.

LITERATURE REVIEW

Penicillin is a bactericidal agent. It works by interfering with the bacterial cell wall synthesis of mucopeptide so that the organism explodes from internal pressures.[2] It affects growing cells rather than resting cells.

Penicillin G and penicillin V are naturally occurring penicillins. Both have similar activity for Gram positive, aerobic microorganisms; however, penicillin G is five to ten times more active against Gram negative microorganisms.[1] Penicillin can be administered orally, parenterally, and as a suppository.

Parenteral administration of penicillin G results in a peak plasma penicillin concentration within 15 to 30 minutes. This value drops rapidly, as penicillin G has a half life of approximately 30 minutes.[1] Because of the short half life, repository compounds have been added to penicillin G to prolong the plasma activity. Procaine and benzathine salts are the best known of these compounds. These salts delay the release of penicillin G from the injection site and give lower, but persistent concentrations of penicillin G in the plasma.[1,2,3]

Procaine penicillin G is formed by adding crystalline procaine salts to penicillin G. N,N'-dibenzylethylenediamine dipenicillin G is formed by adding one mole of ammonium base to two moles of penicillin G. This is also known as benzathine penicillin G. Both procaine pencillin G and benzathine penicilllin G act as local anesthetics.[1]

Penicillin studies were done in the 1950's to compare benzathine penicillin G, procaine penicillin G, and potassium penicilllin G in dogs[14], cattle[4], sheep[13], and swine[13]. Results of these studies showed

that benzathine penicillin G could be detected in the plasma of dogs for eight to 15 days, in cattle for six to nine days, in sheep for five to seven days, and in swine for four to seven days. Procaine penicillin G could be detected for 24 to 48 hours in all species, and potassium penicillin G was detected in the plasma for 12 to 24 hours in the dogs and cattle.

Further studies were done in cattle [5,7] and horses [15]. These studies combined the two repository forms of penicillin G, and showed that a combination of the two repository forms would give a high penicillin blood concentration for 24 hours and then a lower blood concentration for another five to six days. Conclusions made from these studies were: 1) using a combination of the repository forms of penicillin G gave the same penicillin blood concentrations as did giving the two repository forms alone.[5] 2) The combination of benzathine penicillin G and procaine penicillin G can be used either therapeutically or prophylactically.[7,15] 3) If high concentrations of penicillin are wanted in the plasma initially, crystalline or procaine penicillin G should be used.[15]

Residue studies done on benzathine penicillin V, benzathine penicillin G, and procaine penicillin G showed a penicillinemia for 96, 144, and 24 hours respectfully. Penicillinlactias were present for 48, 0, and 24 hours respectfully.[6] Penicillin has been detected 84 days after deep intramuscular injection of benzathine penicillin G in the urine of man.[10,12] In animals, residues of penicillin have been found at the injection site following intramuscular injection up to 45 days post administration.[8,17] Subcutaneous injections will not leave this residue,

thus the reason for the label recommendation of subcutaneous injection. Procaine penicillin G residues have not been found in intermuscular injection sites at 30 days.[11]

Studies in the early 1970's looked at the usage of various penicillins in cattle. These studies noted that potassium penicillin G was present in the blood for 24 hours, and that each 3 million unit increase in penicillin would increase blood levels for 12 hours.[9,16] Sodium penicillin G was therapeutic for two to four hours.[9,16] Procaine penicillin G peaked in concentration at the 4th hour[9,11,16] Benzathine penicillin G again gave prolonged low concentrations of penicillin but therapeutic concentrations were never reached.[9,16] Swine injected with a 50 % benzathine penicillin G, 25 % potassium penicillin, and 25 % procaine penicillin G given subcutaneously at the rate of 20,000 units per kilogram of body weight resulted in penicillin concentrations of 0.04 to 6.14 units per milliliter of serum which was maintained for 96 hours.[21]

The effectiveness of the penicillins against susceptible organisms is dependent upon the minimal inhibitory concentration (MIC) of the organism and the plasma level of penicillin obtained. Recent studies have established the minimal blood concentration of penicillin G needed therapeutically to inhibit penicillin sensitive bacteria is 0.1 to 1 units penicillin per ml of blood.[10,15,16,18,20]

A recent study in cattle showed that benzathine penicillin G and procaine penicillin G given at label dosage was only effective for 4 hours following administration. Five times the label dosage only

provided 12 hours of active blood concentration of penicillin G.[18] Research with horses concluded that the use of benzathine penicillin slowed the decrease of serum concentrations of penicillin down by approximately 48 hours when used in combination with other penicillin products.[19]

The purpose of this study was to determine the duration of various penicillins in the serum of swine.

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MATERIALS AND METHODS

Three groups of pigs (14 pigs per group) were used for this project. They were determined to be healthy as per visual and physical examination. The pigs were kept in confinement and were fed a balanced hog ration during the project.

These trials were done on nursery pigs (5-6 weeks of age), growers (9-10 weeks of age) and on finishers (13-14 weeks of age). During each trial, the pigs were alloted into four treatment groups. These were comprised of: 1) 4 pigs treated with 5000iu/lb Benzathine Penicillin G.[a] 2) 4 pigs treated with 5000 iu/lb Procaine Penicillin G.[b] 3) 4 pigs treated with 5000 iu/lb Procaine and Benzathine penicillin combination.[c] 4) 2 pigs treated with 10,000 iu/lb Procaine and Benzathine penicillin combination.[c] After drawing a zero hour sample, the pigs were given their individual treatment regimen which consisted of one intramuscular injection behind the ear. Blood samples were drawn at 6, 12, 18, 24, 30, 36, and 48 hours. Blood obtained from these animals was allowed to clot before being spun down to remove the serum. Serum samples were frozen until all samples could be analyzed.

The serum samples were analyzed using the Microtiter method. This method of analysis utilizes the use of a Microtiter plate[d] which consists of 8 rows (rows A through H) with each row having 12 wells. This makes a

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a. Bicillin (Wyeth Laboratories)
b. Procaine Penicillin G (Pfizer)
c. Benza-pen (Beecham)
d. Microtiter Plates (Dynatech Laboratories)

total of 96 wells per plate. Each of these wells represents a 20 times 100 mm petri dish used in conventional methods.

A phosphate buffer was prepared by dissolving 13.6 grams of potassium dihydrogen phosphate into 900 ml. of distilled water. The pH of this solution was then adjusted to 4.5 with either 18 N phosphoric acid or 10 N sodium hydroxide. This solution was diluted to a final volume of one liter and sterilized by autoclaving. This produced a 0.1 M phosphate buffer solution.

A standard penicillin preparation was prepared having 4 unit per milliliter actual penicillin activity. Thirty-eight and two tenths milligrams of Sodium penicillin G (potency of 1635 units/mg.)[e] was dissolved in 250 milliliters of 0.1 N HCl to give a standard stock solution of 250 units/ml. Four ml. of this was diluted with 96 ml. of 0.1 M phosphate buffer to give a working standard solution of 10 units/ml. Four ml. of the working standard solution was diluted with 6 ml. of 0.1 M phosphate buffer to give 10 ml. of 4.0 unit/ml. penicillin solution.

A bacterial culture was prepared using Micrococcus luteus It was grown on a standard plate count agar slants and refrigerated. Brain heart infusion broth was inoculated with the culture and incubated for 24 hours at 32 C. The turbid broth was diluted with sterile BHI broth to a Klett reading of 20 Klett unit (KU).

The procedure was done by filling row A with 0.1 ml. of the sample per well with each sample occupying two wells so that each Microtiter

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e. Sodium penicillin G (Pfizer)

plate could hold five samples plus the penicillin standard. The remaining rows (B-H) were filled with 0.05 ml.[f] of the phosphate buffer and then a microdilutor is used to dilute rows A to G leaving out row H as it serves as a control. The microdilutor picks up 0.05 ml. of the solution as it is moved from row to row. This results in the potency of the sample being halved for each successive row. For example, if the penicillin standard has a potency of 4.0 units/ml. in row A, after diluting the penicillin from row A to G, it will have a potency of 2.0 units/ml in row B, 1.0 units/ml in row C, 0.5 units/ml in row D, 0.25 units/ml in row E, 0.125 units/ml in row F, and 0.0625 units/ml in row G.

Five Hundredths ml. of the Micrococcus/ BHI suspension was added to all rows and the microtiter plate is sealed and incubated for 24 hours at 32 C.

The penicillin standard and the antibiotics present in the samples inhibit the growth of the Micrococcus culture. Therefore as the antibiotic decreases from row A to G, the growth of the Micrococcus organism increases from row G to A. The last row at which there is no growth is noted and the potency of that sample can be calculated.

In this study, row D was the last row at which there was no growth for the penicillin standard. Row D had an antibiotic potency of 0.5 units/ml. and 0.5 was used as the multiplying factor.

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f. 0.05 ml. Pipette Droppers (Dynatech Laboratories)

The dilution factors were as follows:

Row A -- 1
Row B -- 2
Row C -- 4
Row D -- 8
Row E -- 16
Row F -- 32
Row G -- 64

If the last row of no growth for a sample is row E, then the antibiotic potency of the sample would be 16 times 0.5 which would be 8 iu/ml.

The procedure should be preformed as aseptically as possible under a hood.

RESULTS

A single injection of the various penicillin compounds used in this study showed several trends over a 48 hour time span. Benzathine penicillin G reached its maximum serum concentration at or near 12 hours post administration. Its initial concentration was roughly one half that of procaine penicillin G, but it did persist at higher concentration levels than procaine penicillin G.

Procaine Penicillin G gave its maximum concentrations around the 6 hour reading. The values of the procaine penicillin then decreased by approximately one half every 6 hours from the initial post administration reading. This trend continued until 24 to 30 hours post administration when the concentration of penicillin was minimal.

The combination of benzathine penicillin G and procaine penicillin G at the rate of 5,000 IU/lb. gave results that were similar to both of the individual penicillins making up this combination. Its serum concentration peaked around the 6th hour following post administration. However, its maximum concentration was aproximately 60 % that of procaine penicillin G alone, but it was higher than that of benzathine penicillin alone. The serum concentrations past the 24 hours post administration were similar to that of benzathine penicillin alone.

The higher dosage (10,000 IU/lb.) of the combination of procaine penicillin G and benzathine penicillin G produced a pattern similar to that of the lower dosage of the combination penicillins. This dosage gave results that were nearly identical to procaine penicillin G over the

first 24 hours, and nearly identical to benzathine penicillin G over the second 24 hours.

The following tables 1 through 4 show the actual study results.

TABLE 1: Penicillin Serum Levels of Nursery Pigs Receiving a Single IM Injection of Various Penicillin Compounds.

ID	WT (lb)	TRMT	CON	Units of penicillin per ml. of serum 6 hr.	12 hr.	18 hr.	24 hr.	30 hr.	36 hr.	48 hr.
		a								
1	41	BPG	0	2	4	3	1	1	1	0.75
2	40	BPG	0	3	3	2	2	0.5	0.5	0.5
3	40	BPG	0	4	4	4	4	1	0.5	1
4	42	BPG	0	4	4	4	4	1	1	1
		AVERAGE		3.25	3.75	3.25	2.75	0.88	0.75	0.81
		SD		0.96	0.5	0.96	1.5	0.25	0.29	0.24
5	41	PPGb	0	4	4	3	2	0	0	0
6	41	PPG	0	8	4	3	1	0	0	0
7	40	PPG	0	8	2	1	0.5	0	0	0
8	41	PPG	0	8	2	1	1	0	0	0
		AVERAGE		7	3	2	1.13	0	0	0
		SD		2	1.15	1.15	0.63	0	0	0
		c								
9	42	LC	0	6	4	1	1	1	1	0.5
10	41	LC	0	4	2	2	1	0.5	0.5	0.5
11	40	LC	0	4	2	1.5	1	0.75	0.5	0.5
12	40	LC	0	4	3	2	2	0.75	0.5	0.5
		AVERAGE		4.5	2.75	1.63	1.25	0.75	0.63	0.5
		SD		1	0.96	0.48	0.5	0.20	0.25	0
		d								
13	42	HC	0	4	4	2	2	2	1	1
14	42	HC	0	8	3	2	2	0.5	0.5	0.5
		AVERAGE		6	3.5	2	2	1.25	0.75	0.75
		SD		2.83	0.71	0	0	1.06	0.35	0.35

a. Benzathine Penicillin G (5,000 IU/lb)
b. Procaine Penicillin G (5,000 IU/lb)
c. Benzathine and Procaine Penicillin G Combination (5,000 IU/lb)
d. Benzathine and Procaine Penicillin G Combination (10,000 IU/lb)

TABLE 2: Penicillin Serum Levels of Grower Pigs Receiving a Single IM Injection of Various Penicillin Compounds

ID	WT (lb)	TRMT	CON	Units of penicillin per ml. of serum						
				6 hr.	12 hr.	18 hr.	24 hr.	30 hr.	36 hr.	48 hr.
		a								
1	62	BPG	0	4	4	3	1	0.5	0.5	0.5
2	55	BPG	0	2	3	2	2	1	0.5	0.5
3	55	BPG	0	4	4	2	1.5	1	0.5	0.5
4	80	BPG	0	2	4	4	3	1	0.5	0.5
		AVERAGE		3	3.75	2.75	1.86	0.88	0.5	0.5
		SD		1.15	0.5	0.96	0.85	0.25	0	0
		b								
5	82	PPG	0	4	4	2	1.5	0.5	0	0
6	75	PPG	0	8	4	3	1	0	0	0
7	40	PPG	0	8	4	2	1	0	0	0
8	100	PPG	0	6	8	4	2	0.5	0	0
		AVERAGE		6.5	5	2.75	1.38	0.25	0	0
		SD		1.91	2	0.96	0.48	0.29	0	0
		c								
9	62	LC	0	4	2	2	2	1	0.5	0.5
10	48	LC	0	4	2	2	2	0.5	1	0.5
11	65	LC	0	2	2	1	1	1	0.5	0.5
12	75	LC	0	4	2	2	1	1	0.5	0.5
		AVERAGE		3.5	2	1.75	1.5	0.88	0.63	0.5
		SD		1	0	0.5	0.58	0.25	0.25	0
		d								
13	90	HC	0	8	4	2	1	1	1	0
14	92	HC	0	8	4	1	0.75	0.5	0.5	0.5
		AVERAGE		8	4	1.5	0.88	0.75	0.75	0.25
		SD		0	0	0.71	0.18	0.35	0.35	0.35

a. Benzathine Penicillin G (5,000 IU/lb)
b. Procaine Penicillin G (5,000 IU/lb)
c. Benzathine and Procaine Penicillin G Combination (5,000 IU/lb)
d. Benzathine and Procaine Penicillin G Combination (10,000 IU/lb)

TABLE 3: Penicillin Serum Levels of Finish Pigs Receiving a Single IM Injection of Various Penicillin Compounds

ID	WT (lb)	TRMT	CON	Units of penicillin per ml of serum						
				6 hr.	12 hr.	18 hr.	24 hr.	30 hr.	36 hr.	48 hr.
			a							
6	100	BPG	0	1	4	2	2	0.5	0.5	0.5
7	120	BPG	0	2	1	1	1	1	1	1
9	85	BPG	0	1.5	1	1	0.5	1	1	1
12	60	BPG	0	4	2	1.5	1	1	1	0.5
		AVERAGE		2.13	2	1.38	1.13	0.88	0.88	0.75
		SD		1.31	1.41	0.48	0.63	0.25	0.25	0.29
			b							
3	113	PPG	0	8	4	2	1	0.5	0	0
5	103	PPG	0	8	2	1	0.5	0	0	0
8	75	PPG	0	6	2	2	1	1	0.5	0.5
14	90	PPG	0	8	4	2	0.5	0.5	0.5	0.5
		AVERAGE		7.5	3	1.75	0.75	0.5	0.25	0.25
		SD		1	1.15	0.5	0.29	0.41	0.29	0.29
			c							
1	93	LC	0	8	4	2	2	1	1	0.5
2	145	LC	0	8	4	4	2	2	0	0
10	80	LC	0	4	2	1	0.5	1	1	1
11	95	LC	0	4	3	1	1	1	1	0.5
		AVERAGE		6	3.25	2	1.38	1.25	0.75	0.5
		SD		2.31	0.96	1.41	0.75	0.5	0.5	0.41
			d							
4	105	HC	0	8	4	4	2	1	1	0.5
13	80	HC	0	8	4	3	1	1	1	1
		AVERAGE		8	4	3.5	1.5	1	1	0.75
		SD		0	0	0.71	0.71	0	0	0.35

a. Benzathine Penicillin G (5,000 IU/lb)
b. Procaine Penicillin G (5,000 IU/lb)
c. Benzathine and Procaine Penicillin G Combination (5,000 IU/lb)
d. Benzathine and Procaine Penicillin G Combination (10,000 IU/lb)

TABLE 4: Combined Penicillin Serum Levels of Nursery, Grower, and Finishing Pigs after Receiving a Single IM injection of a Penicillin Compound.

		Units of penicillin per ml of serum						
AGE	TRMT	6 hr.	12 hr.	18 hr.	24 hr.	30 hr.	36 hr.	48 hr.
	[a]							
Nursery	BPG	3.25	3.75	3.25	2.75	0.88	0.75	0.81
Grower	BPG	3	3.75	2.75	1.88	0.88	0.5	0.5
Finish	BPG	2.13	2	1.38	1.13	0.88	0.88	0.75
	AVERAGE	2.79	3.17	2.46	1.92	0.88	0.71	0.69
	[b]							
Nursery	PPG	7	3	2	1.13	0	0	0
Grower	PPG	6.5	5	2.75	1.38	0.25	0	0
Finish	PPG	7.5	3	1.75	0.75	0.5	0.25	0.25
	AVERAGE	7	3.67	2.17	1.08	0.25	0.08	0.08
	[c]							
Nursery	LC	4.5	2.75	1.63	1.25	0.88	0.75	0.5
Grower	LC	3.5	2	1.75	1.5	0.88	0.63	0.5
Finish	LC	6	3.25	2	1.38	1.25	0.75	0.5
	AVERAGE	4.67	2.67	1.80	1.38	1.0	0.71	0.5
	[d]							
Nursery	HC	6	3.5	2	2	1.25	0.75	0.75
Grower	HC	8	4	1.5	0.88	0.75	0.75	0.25
Finish	HC	8	4	3.5	1.5	1	1	0.75
	AVERAGE	7.33	3.83	2.33	1.46	1	0.83	0.58

a. Benzathine Penicillin G (5,000 IU/lb)
b. Procaine Penicillin G (5,000 IU/lb)
c. Benzathine and Procaine Penicillin G Combination (5,000 IU/lb)
d. Benzathine and Procaine Penicillin G Combination (10,000 IU/lb)

DISCUSSION

Penicillin is widely used in the swine industry as a treatment and/or prevention for many swine diseases. Because of the extremely short blood level achieved with sodium or potassium penicillin G, almost all penicillin products used in swine are a penicillin molecule attached to a repository salt such as procaine, benzathine, or a combination of the two. Procaine penicillin G should be redosed after 24 hours as its serum concentration after this time is minimal.

The long acting penicillin product composed of procaine penicillin G and benzathine penicillin G is a valid combination; however, the dosage should be doubled that used for procaine penicillin (increased to 10,000 iu/lb.), to achieve a similiar initial blood level. The doubled dosage gives a similiar initial blood level from the procaine penicillin G and the benzathine penicillin G produces an extended lower penicillin level. At this increased dosage, there is a similiar higher initial serum concentration of penicillin with a slow persistent level of penicillin concentration out to at least 48 hours. The lower dosage of the combination product is of value in the treatment and prevention of some swine pathogens, due to the low minimum inhibitory concentration of the organisms.

Recomendations coming from this study are:

1) The combination penicillins are a valid treatment for swine pathogens if the dose is based upon the procaine penicillin level. They may be indicated as a prophylactic treatment since the blood level of penicillin will be

maintained for an extended time and this would preclude treating pigs at 24 hours.

2) Procaine penicillin would be the choice when high serum concentration of penicillin are needed to treat against a specific swine pathogen. It should be redosed after 24 hours.

3. The cost of procaine penicillin and procaine/benzathine penicillins are variable. When the cost per unit of penicillin is similar, the injection of the combination form at double the dose of procaine penicillin would result in a similar initial blood concentration and an extended level and preclude the need for redosing the pig at 24 hours.

4. Results from this study showed that therapeutic levels of penicillin can be obtained with benzathine penicillin in swine to effectively cover the minimum inhibitory concentration of many swine pathogens. Examples of some minimum inhibitory concentrations for bacteria are: 1) Pasturella sp. .5 to 2 iu/ml.; 2) Corynebacterium renale .0001 to 1 iu/ml.; 3) Staphylococcus aureus .008 to 2.64 iu/ml.; and 4) Streptococcus .0033 to .33 iu/ml..

The minimum inhibitory concentration for the Micrococcus luteus in this study was 0.5 iu/ml of penicillin. For maximum therapeutic effectiveness further studies should be conducted to determine the minimum inhibitory concentration of penicillin for major swine pathogens.

Determination of the Magnitude and Duration of Penicillin Serum Levels in Swine Following a Single Intramuscular Injection of Procaine Penicillin G and of Benzathine Penicillin G

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ABSTRACT

Nursery, grower, and finishing pigs were injected with benzathine penicillin G, procaine penicillin G, or a combination of the two. In each age group, the pigs were randomly divided and received a single intramuscular injection of one of the following regimens: 1) 5,000 IU/lb. of benzathine penicillin G; 2) 5,000 IU/lb. of procaine penicillin G; 3) 5,000 IU/lb. combination of procaine penicillin G and benzathine penicillin G; and 4) as per number 3 at the dosage of 10,000 IU/lb..

A pre-injection blood sample was drawn, and then samples were drawn at 6, 12, 18, 24, 30, 36, and 48 hours post administration of the penicillin products. The samples were analyzed using the Microtiter method.

Results from the study showed that the combination penicillin form acted as the two individual forms which make it up. Benzathine penicillin G reaches moderate serum concentrations but will persist over an extended time period. Procaine penicillin G reaches peak serum concentrations quickly, but then decreased quickly over a 24 hour period.

Procaine penicillin G was shown to be the repository salt penicillin of choice when higher serum concentrations of penicillin are needed. Procaine penicillin G and Benzathine penicillin G combined are a valuable therapeutic agent, however, the combination of penicillins should be administered at twice the dosage used for procaine penicillin G.