Hetacillin - A New Approach to Mastitis Control

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The introduction of a totally new antibiotic preparation for the treatment and control of mastitis is sufficiently infrequent as to be of importance to the bovine practitioner.

The use of a new drug to best advantage requires that the clinician have full knowledge of what to expect of it, and indeed, to be aware of its limitations. The purpose of this report is to discuss a clinical field study using potassium hetacillin in lactating cows with varying degrees and clinical manifestations of mastitis.

At the time the study was initiated, we defined what we believe to be the criteria of an ideal intramammary infusion: Highly active against Gram positive organisms; Highly active against Gram negative organisms; Bactericidal activity; Non-irritant to udder tissue; and, Elimination of residual antibiotic not undule prolonged.

Preclinical studies demonstrated that potassium hetacillin had the potential to meet all these criteria, since it was non-irritant to the udder, and milked out in less than 72 hours in both normal cows and cows with mastitis.

Potassium hetacillin, a derivative of 6-aminopenicillanic acid, rapidly hydrolyses to ampicillin in the blood and in body fluids. Ampicillin provides bactericidal activity against a broad range of both Gram-positive and Gram-negative pathogens, making it truly broad spectrum in character. The bactericidal action of ampicillin is believed to result from inhibition of biosynthesis of cell wall mucopeptides, and occurs during the stage of active bacterial multiplication.

Microbiology:

The hetacillin provides excellent bactericidal activity against Gram-positive and Gram-negative mastitis pathogens is clear from Table 1 which indicates *in vitro* expectancy based upon two measurements i.e., average minimum inhibitory concentrations by tube dilution technique, and the percent of isolates found to be susceptible by the single disc method. It should be noted that ampicillin susceptibility discs 10 mcg. should be used to determine the susceptibility of organisms to hetacillin.

Since it is inactivated by penicillinase, hetacillin is not effective against penicillin resistant *staphylococcus aureus.*

Table 1

In Vitro Activity of Hetacillin

Organism	Avg. Minimum Inhibitory Concentration (mcg./ml.)	% of Isolates Susceptible
Strep agalactiae	0.05	98.1
Strep dysgalaciae	0.05	96.1*
Strep uberis	0.78	
Staph aureus	0.1 (pen sensitive)	57.1**
Staph species	0.025	81.8
E. coli	3.0 - 5.0	74.4

*Identified as strep non-agalactiae
**Includes penicillin resistant *staph aureus*

Methods:

As is usual in this type of study, a number of clinical investigators contributed clinical case histories. They were located in several major milk producing areas, and all were experienced dairy practitioners.

The drug was supplied as Hetacin K (potassium hetacillin) for intramammary infusion, each 10 ml. disposable syringe containing potassium hetacillin equivalent to 62.5 mg. ampicillin activity in a stable peanut oil gel.

The study protocol supplied to each investigator stressed important aspects of the study;

1. Two pretreatment quarter samples were required to establish a diagnosis.
2. Two post treatment (18 to 21 days) quarter samples must be cultured.
3. There must be no adjunctive therapy, either parenteral or by intramammary infusion.
4. Somatic cell count or CMT score must be recorded before and after treatment.

All these were important because of the method we proposed to evaluate response to treatment.

There are four ways that a response to treatment may be evaluated: (1) Demonstrated elimination of the pathogen; (2) Significant reduction of cell count; (3) Observed reduction of inflammation; and (4) Milk observed to be normal.

The latter two are invariably used by the dairyman; the practitioner can, and should, use all four.

For the purpose of this study, subjective observations were rejected as a valid means of evaluating response, and the results are discussed solely in terms of elimination of the pathogen as determined by recognized culture techniques, and a measurement of the effect upon the somatic cell count in treated quarters.

Results:

Although well over 1,000 quarters were treated in the course of the study, included and analyzed in the summary tables are only those cases which conformed to the protocol in all material respects, i.e., confirmed diagnosis, no adjunctive therapy, duplicate post-treatment samples.

To demonstrate the elimination of the pathogen in lactating cows is clearly the most severe test of a therapeutic agent. To claim that the pathogen has been eliminated, two separate quarter samples taken 18 to 21 days following treatment must be free of the original organism. In clinical cases, Dodd (1) states that in his experience this will occur in only 33% of treated lactating cows.

With this in mind, Table 2 summarizes the results of the study as measured by the elimination of the pathogen. As might be expected, streptococcal infections proved easier to eliminate than staphylococcal or Gram-negative infections but an overall bacterial cure rate of 81% must be considered remarkable.

Investigators were asked to record in each case the duration and clinical manifestations as acute, acute flare-up of a chronic condition, chronic or subclinical. To the extent that this was done, and omitting minor species, the data are expressed from this aspect in Table 3.

It should be reiterated in respect to this table that none of these cases received any adjunctive therapy of any kind.

Table 3

Hetacillin – Summary of Results by Clinical Manifestation

Category	No. of Cases	Pathogen Eliminated	Pathogen Not Eliminated	% Eliminated
Acute	52	36	16	69
Acute flare-up	31	19	12	61
Chronic	124	102	22	82
Subclinical	170	151	19	89
Totals	377	308	69	82

Herd Control Studies:

It is generally agreed that herds heavily infected with *A. agalactiae* are the only suitable subjects in which to attempt rapid reduction of infection levels, or actual eradication, by treatment of cows while in milk.

Two types of control programs were used in this study:

1. Split herd method—A quarter sample survey of the entire herd is followed by treatment of all cows showing one or more positive quarters in one half of the herd. The other half of the herd serves as a control. After three weeks, and following another herd survey, the positive cows in the second group are similarly treated. The herd status is then determined by an additional herd survey at a suitable interval following treatment (18-21 days).

2. The so-called "blitz" method—Following a quarter sample herd survey, all cows showing one or more positive quarters are given a full course of treatment followed by another survey in three weeks.

Table 2

Hetacillin – Summary of Results. Elimination of Pathogen.

Pathogen	Total Cases	Pathogen Eliminated	Pathogen Not Eliminated	% Eliminated
Streptococcus agalactiae	267	251	16	94
Streptococcus nonagalactiae	29	23	6	79
Streptococcus dysgalactiae	59	47	12	80
Streptococcus uberis	11	11	0	100
Staphylococcus aureus	137	84	53	61
Staphylococcus species	43	37	6	86
E. coli	43	27	16	63
Klebsiella	23	18	5	78
Proteus	7	6	1	86
Totals	619	504	115	81

Two herds were treated by each method to test the feasibility of eradicating *Strep agalactiae* infection using potassium hetacillin. Table 4 summarizes these results.

Table 4

Hetacillin – Herd Studies to Control Strep Agalactiae

	Method	Infected Quarters Pre-treatment	Post-treatment	% Cleared
Herd N	Split herd	58	1	98.3
Herd F	Split herd	40	0	100.0
Herd B	"Blitz"	61	5	91.8
Herd T	"Blitz"	52	0	100.0

Response in Somatic Cell Count:

As the second measurement of response to treatment, these studies included a very careful assessment for each quarter, of the cell count before and after treatment. Some were determined by direct somatic cell count, others by C.M.T. score. For purposes of analyses, all have been converted to C.M.T. scores by recognized standards (2). Pretreatment samples were evaluated immediately prior to treatment; post-treatment samples 18 to 21 days after completion of treatment.

Table 5 summarizes the clinical response to treatment as measured by cell count, and these reductions in CMT score, analyzed statistically, were all found to be highly significant (P= .001).

Table 5

Hetacillin – Clinical Response as Measured by CMT Scores

Pathogen	Total Cases	CMT Scores (arithmetic mean) Pre-treatment	Post-treatment
Strep agalactiae	245	1.97	0.76
Staph aureus	123	2.02	1.16
E. coli	46	2.54	1.01
Strep dysgalactiae	59	1.89	0.91

Discussion:

Potassium hetacillin was shown to be a highly effective treatment for all forms of mastitis caused by Gram-positive as well as Gram-negative organisms. *In vitro* data clearly indicate the high degree of susceptibility of common mastitis pathogens to hetacillin.

While *in vitro* susceptibility testing plays a useful part in the selection of the antibiotic of choice, the correlation between *in vitro* and *in vivo* results is the ultimate factor determining a practitioners' choice of therapy.

Table 6 expresses this relationship and indicates a high degree of correlation between *in vitro* results and the clinician's expectations.

The ability of therapy to eliminate the causal pathogen must be the ultimate criterion of efficacy, and an antibiotic that has the versatility to eliminate 94% of *Streptococcus agalactiae* infections as well as 63% of the *E. coli* must be considered unique.

Table 6

Hetacillin – Correlation Between In Vitro and In Vivo Results

Organism	In Vitro Susceptibility No. of Isolates	% Susceptible	In Vivo Bacteriological Cure No. of Cases	% Cured
S. agalactiae	208	98	267	94
S. nonagalactiae	102	96	99	82
Staph aureus	117	57	137	61
Staph spp.	99	82	43	86
E. coli	121	74	46	63

Dairyman interest in herd control programs has heightened since the promulgation of laws with "teeth," prohibiting the marketing of milk with a high leucocyte count. This, coupled with the realization that infected cows are producing at least 10% below their potential, makes herd treatment, even the "blitz" type, not only more attractive to the dairyman, but also a matter of pure economic good sense.

In the four herd control studies the bacteriological cure rate against *Streptococcus agalactiae* was 97.2%, an excellent result considering the delays in treatment imposed by the experimental design, and the fact that a number of these cows had failed to respond to other medication.

Potassium hetacillin significantly reduced CMT scores on post-treatment samples against all pathogens signalling excellent clinical response to therapy.

Summary:

In a comprehensive study involving several hundred cases, Hetacin K (potassium hetacillin) for intramammary infusion was shown to be an effective treatment for mastitis as measured by bacteriological cure rate, and reduction of somatic cell count.

Hetacillin was highly effective in acute, chronic and subclinical forms of mastitis caused by all the major mastitis bacterial pathogens, and gave very gratifying results when used on a herd control basis.

Hetacillin offers the dairy practitioner a new single antibiotic providing truly broad spectrum coverage.

References

1. Dodd, F. H., National Mastitis Council Meeting, 1973; p. 11. - 2. Schalm, O. W., Bovine Mastitis, p. 139.