Diminished Hypercalcemic Response to Parathyroid Extract in Prepartum Cows

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Abstract

Parathyroid extract was administered to five cows shortly before and after parturition in addition to postpartal injections only in two other cows. Plasma calcium concentration was measured in each experiment before and after administration of the extract. The postpartal response to parathyroid extract, as assessed by elevation of plasma calcium concentration, occurred more consistently and appeared to be greater than that observed before parturition. The possible mechanisms responsible for diminished prepartal responsiveness and its potential significance in relation to parturient paresis are discussed.

Introduction

Since the discovery that parturient paresis was accompanied by hypocalcemia (16), parathyroid function in parturient cows has received widespread attention. Dryerre and Greig (7) suggested that the hypocalcemia of the syndrome might be the result of a parathyroid insufficiency. Recent investigations have conclusively refuted this hypothesis. Ultrastructural characteristics of parathyroid glands from cows with parturient paresis were indicative of active hormone synthesis (5), and the parathyroid response to hypocalcemia in diseased cows, as assessed by plasma hormone concentration, was equal to that of control cows (20). The occurrence of severe hypocalcemia in parturient cows despite increased parathyroid activity directs attention to the response of hormone sensitive target tissues. Parathyroid extract administration is accompanied by a rise of plasma calcium concentration in nonparturient cows (12, 13, 19), but not in parturient cows (13). The frequent occurrence of hypocalcemia in parturient cows together with the absence of an overt response to parathyroid extract led Hibbs et al. (12) to suggest that the hormone may be rendered temporarily inactive by some metabolic condition in the tissues at parturition. Later, Jackson et al. (13) proposed that the target tissues of parathyroid hormone may be nonresponsive in parturient cows. Assessment of the response of parturient cows to parathyroid extract on the basis of plasma calcium concentration is problematic since the decline in plasma calcium associated with the onset of lactation is apt to mask any hypercalcemic effects of the extract. In view of this, we have evaluated the response to parathyroid extract of individual cows both before and after parturition.

Experimental Procedures

A dose of 5,000 USP units of parathyroid extract was administered intramuscularly to five cows before and after parturition (Table 1). An additional two cows were studied after parturition only (Table 1). An attempt was made to perform preparturient injections within the last week of gestation, but failure to predict accurately the day of parturition led to an interval of 8 to 19 days between the experiment and calving. Postpartum experiments were 3 to 12 days following parturition to avoid the hypocalcemic period near calving. Blood for calcium analysis was collected by venapuncture of the jugular vein into heparinized vials at 24, 16, 8, and 0 h before extract injection at 0800 and at 2, 4, 6, 8, 12, 16, 20, 24, and 32 h afterwards. Following

Received September 28, 1972.

1 This work supported in part by USPHS grant no. AM-16,983.
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4 Parathyroid injection, USP, was donated by Eli Lilly and Company, Greenfield, Indiana 46140.
RESPONSE TO PARATHYROID EXTRACT

Table 1. Dates of experiments.

<table>
<thead>
<tr>
<th>Cow no.</th>
<th>Age (yr)</th>
<th>Body weight (kg)</th>
<th>Expected date of parturition</th>
<th>Date of parturition</th>
<th>Prepartal experiment</th>
<th>Postpartal experiment</th>
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<tbody>
<tr>
<td>146</td>
<td>4.5</td>
<td>396</td>
<td>4-21-69</td>
<td>4-16-69</td>
<td>4-15-69*</td>
<td>4-22-69</td>
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<td>153</td>
<td>4.25</td>
<td>395</td>
<td>4-26-69</td>
<td>5-01-69</td>
<td>4-22-69</td>
<td>5-07-69</td>
</tr>
<tr>
<td>073</td>
<td>7.25</td>
<td>505</td>
<td>5-02-69</td>
<td>5-02-69</td>
<td>5-04-69</td>
<td>5-07-69</td>
</tr>
<tr>
<td>135</td>
<td>5</td>
<td>487</td>
<td>5-14-69</td>
<td>5-18-69</td>
<td></td>
<td>5-07-69</td>
</tr>
<tr>
<td>112</td>
<td>6</td>
<td>458</td>
<td>5-24-69</td>
<td>5-19-69</td>
<td>5-11-69</td>
<td>6-01-69</td>
</tr>
<tr>
<td>157</td>
<td>4.5</td>
<td>405</td>
<td>6-01-69</td>
<td>6-03-69</td>
<td>5-18-69</td>
<td>6-06-69</td>
</tr>
<tr>
<td>132</td>
<td>5.5</td>
<td>449</td>
<td>6-05-69</td>
<td>6-06-69</td>
<td>5-18-69</td>
<td>6-05-69</td>
</tr>
</tbody>
</table>

* Cow 146 was calving during the first experiment, 13 h after injection of parathyroid extract.
† Developed parturient paresis at parturition.
‡ First experiment missed because of stillbirth 10 days before expected calving date.
§ Postpartal experiment delayed due to illness. Parturient paresis developed 17 h postpartum, but responded to intravenous and oral calcium therapy. Five days after parturition, left displacement of the abomasum and ketosis were diagnosed. Recovery followed surgical correction of the displacement and intravenous glucose infusion. The cow was completely recovered before the second experiment was begun.

PTT ADMINISTRATION

Before Parturition

After Parturition

Cow 157

PLASMA CALCIUM

mg/100 ml

TIME, hours

by the mean ± 2 SD of four samples taken at 8 h intervals during the 24 h immediately before extract administration. Calcium values above the shaded areas are considered as an indication of a response to the parathyroid extract. Responses are more consistent and appear somewhat greater in the postpartal period.

Centrifugation the plasma was separated and stored frozen. Plasma calcium concentration was determined fluorometrically by the method of Keprner and Hercules (14) as modified by G. K. Turner Associates, 2425 Pulgas Avenue, Palo Alto, California. Cows were from the same herd and of the Jersey breed. Before calving the cows were housed in box stalls and fed a ration of varying amounts (depending on availability) of alfalfa hay, alfalfa and timothy silage, corn silage, and grain-concentrate mixtures. After parturition husbandry was similar except that the cows were allowed access to grass pasture during daylight.

Results and Discussion

Plasma calcium response to parathyroid extract administration before parturition was diminished compared to that observed after parturition (Fig. 1 and 2). A rise in plasma calcium concentration above the 95% confidence limits of the mean preinjection concentration indicated a response to the extract. In the prepartal period response was slight in three of five cows whereas a definite response was observed in seven of seven cows after parturition (Fig. 1 and Table 2). Grouping of data from individual cows in both prepartal and postpartal experiments illustrates the magnitude of the difference in response in the two periods (Fig. 2). In the postpartal period the
preinjection plasma calcium concentration was less than that of the prepartal period but rose higher following parathyroid extract administration than that during the prepartal experiments.

Due to happenstance, parathyroid extract was administered to cow 146 just 13 h before parturition (Fig. 3). At this time the decline of plasma calcium concentration associated with onset of lactation already had begun. Plasma calcium declined at a steady rate for 8 h following injection. By 12 h postinjection the fall in calcium concentration had halted, and an increase was observed 4 h later followed by a decrease during the ensuing 8 h (Fig. 3). Subsequently, the plasma calcium concentration gradually increased, returning to the normal range within 40 h. Changes in plasma calcium concentration in this cow in relation to parturition are typical of many parturient cows with the exception of the transitory rise in concentration which occurred during the declining phase. The cessation of the fall in concentration at 12 h postinjection and the increase at 16 h postinjection temporally coincide with maximum plasma calcium concentration following parathyroid extract administration to either prepartal or postpartal cows, i.e., 12 to 20 h postinjection (Table 2). A similar change in rate of plasma calcium decline in one cow following parathyroid extract administration is apparent upon examination of data reported by Jackson et al. (13, see Fig. 2, cow B-4). In our opinion, the change in rate of decline of plasma calcium concentration in these two parturient cows at the expected time following parathyroid extract administration represents a response to parathyroid extract.

The responsiveness of parathyroid target or-

### Table 2. Response of prepartal and postpartal cows to parathyroid extract administered intramuscularly.

<table>
<thead>
<tr>
<th>Cow no.</th>
<th>Prepartal</th>
<th>Postpartal</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Plasma calcium (mg/100 ml)</td>
<td>response* time (h)</td>
</tr>
<tr>
<td></td>
<td>preinjection x ± SD</td>
<td>postinjection (max. value)</td>
</tr>
<tr>
<td>157</td>
<td>10.2 ± 0.20</td>
<td>11.4</td>
</tr>
<tr>
<td>112</td>
<td>9.8 ± 0.26</td>
<td>10.6</td>
</tr>
<tr>
<td>073</td>
<td>10.0 ± 0.29</td>
<td>11.1</td>
</tr>
<tr>
<td>153</td>
<td>10.2 ± 0.39</td>
<td>10.6</td>
</tr>
<tr>
<td>132</td>
<td>9.7 ± 0.34</td>
<td>10.1</td>
</tr>
<tr>
<td>146</td>
<td>. . .</td>
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</tr>
<tr>
<td>135</td>
<td>. . .</td>
<td>. . .</td>
</tr>
</tbody>
</table>

* Number of hours after injection at which maximum concentration of plasma calcium was observed.
* Develop parturient paresis at parturition.
* The results in the experiments were interpreted as a lack of response since the maximum calcium concentration attained fell within the 95% confidence limits of the mean preinjection plasma calcium concentration.
* Experiments not done in prepartal period. Cow 146 calved during the attempted prepartal experiment.

Journal of Dairy Science Vol. 56, No. 8
gans remains an issue for consideration in regard to parturient paresis. Diminished response in the prepartal period supports the possibility that target organ response may play a role in the development of hypocalcemia at parturition, but such a role, if it exists, is likely to be more complex than previously appreciated. Previous investigators have concluded that parturient cows are not responsive to parathyroid hormone. However, our experiment with a parturient cow (Fig. 3) and further evaluation of previous data (13) demonstrate that this is not the case in all instances. Furthermore, the presence of a prepartal response in some cows, which intensifies during the pre to postpartum interval, suggests a suboptimal response of the parturient cow as a more plausible likelihood than a complete absence of response. If we presume that most parturient cows exhibit some degree of response to parathyroid hormone, a hypothesis then may evolve proposing a lesser degree of response in cows developing parturient paresis. Although our data relating to this proposition are scanty, two statements can be made. First, a diminished prepartal response is not necessarily followed by parturient paresis. Secondly, the prepartal (cow 112) and postpartal (cows 112 and 135) responses of cows, which developed parturient paresis, were not less than those of the other cows (Fig. 1 and Table 2). In our opinion, diminished parathyroid target organ response is not likely to be a primary etiological factor in parturient paresis since it appears to be a feature associated with parturition, per se. However, response of target tissues may still contribute to the development of hypocalcemia. The naturally high calcium diet of the prepartal period appears to render the parturient cow reliant upon calcium absorption from the gut for the replenishment of blood calcium (18). In the event of a temporary interruption of calcium absorption at parturition, a sluggish response of the bone to the increased concentration of parathyroid hormone in the blood could impede replacement of blood calcium lost into the milk and accelerate the development of hypocalcemia.

The factors contributing to a diminished prepartal response to parathyroid extract are not known. However, examination of results from other experimental situations offers possibilities for consideration. Parathyroid hormone exerts its hypercalcemic effect by increasing the liberation of calcium from bone (9), by promoting intestinal calcium absorption (23), and by increasing the renal tubular reabsorption of calcium (15). Since urinary calcium excretion in cows is small and does not change in relation to parturition (22), it seems unlikely that a refractory renal response would contribute significantly. However, several hormones have influenced the effect of parathyroid hormone on bone. Calcitonin (1), adrenal corticosteroids (24), and estrogens (2) are antagonistic to the parathyroid effect while cholecalciferol appears to enhance it (10). Previous work has related all of these factors to either parturition or parturient hypocalcemia. Calcitonin has been implicated as a contributing factor in parturient hypocalcemia (4); estrogen secretion increases just before parturition (8); and concentration of hydrocortisone was increased in hypocalcemic parturient cows (17). Pharmacologic doses of vitamin D will reduce the incidence of parturient paresis (11); and 25-hydroxycholecalciferol, a metabolite of the vitamin produced in the liver (6, 21), offers promise of efficacy at greatly reduced dose rates (3). Any or all of these factors conceivably could contribute to the diminished hypercalcemic response to parathyroid extract in prepartal cows, but definite association of any of them with the observed phenomenon awaits further investigation.

References

(7) Dryerre, H., and J. R. Greig. 1928. Further


