Hyperbilirubinemia in Sick Cattle

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ABSTRACT

Hyperbilirubinemia was present in 387 out of 1279 sick cattle admitted to the clinic of the Ontario Veterinary College. One hundred and ninety five of these had a total serum bilirubin of 17 μmol/L or greater. Clinical records, laboratory data and when available, pathology reports from these 195 animals were examined in an attempt to explain the reason for the high bilirubin levels. The hyperbilirubinemia in 187 of these was mainly due to an increase in unconjugated bilirubin. Jaundice, liver disease or anemia was not a feature and alkaline phosphatase was not elevated. The 195 animals with hyperbilirubinemia suffered from a variety of diseases that seemingly were unrelated to the increased bilirubin. The most frequently described signs were anorexia and rumen stasis. Liver disease was diagnosed in eight animals and in these clinical jaundice, and increased conjugated bilirubin and alkaline phosphatase was a feature. It was concluded that hyperbilirubinemia occurred in many diseases of cattle and in most instances was related to a failure of the liver to remove unconjugated bilirubin from the serum rather than to a failure of the liver to excrete conjugated bilirubin.

Key words: Cattle, hyperbilirubinemia, bilirubin, jaundice, alkaline phosphatase, cholesterol, aspartate amino transferase, anorexia and rumen stasis.

RÉSUMÉ

Au cours d'une période de 33 mois, les auteurs ont détecté une hyperbilirubinémie chez 387 des 1279 bovins malades, admis à la clinique du Collège Vétérinaire de l'Ontario. Chez 195 d'entre eux, la bilirubine sérique totale s'avéra égale ou supérieure à 17 μmol/L. On examina les dossiers cliniques et les résultats de laboratoire, ainsi que les rapports de pathologie disponibles de ces bovins, dans un effort visant à expliquer la raison de cette hyperbilirubinémie. Chez 187, elle résultait surtout d'une augmentation de la bilirubine non conjuguée; l'ictère, une maladie du foie ou l'anémie ne constituaient pas un trait caractéristique et la phosphatase alcaline n'accusait aucune élévation. Les 195 bovins atteints d'hyperbilirubinémie souffraient d'une variété de maladies apparemment non reliées à l'élévation de la bilirubine. L'anorexie et une stase du rumen correspondaient aux signes cliniques prédominants. Huit bovins souffraient de maladies hépatiques qui se caractérisaient par de l'ictère, ainsi que par une élévation de la bilirubine conjuguée et de la phosphatase alcaline. Les auteurs conclurent que l'hyperbilirubinémie accompagnait plusieurs maladies de ces bovins et que, la plupart du temps, elle résultait plutôt de l'incapacité du foie d'éliminer du sérum la bilirubine non conjuguée que de son inhabilité d'excréter la bilirubine conjuguée.

Mots clés: bovins, hyperbilirubinémie, ictère, phosphatase alcaline, cholestérol, aspartate-transaminase, anorexie, stase du rumen.

INTRODUCTION

Hyperbilirubinemia is usually considered to result from either overproduction or underexcretion of bilirubin (1,2). The factors causing hyperbilirubinemia are complex and in any one case are likely to be multiple (1,2,3). Overproduction as exemplified by hemolysis may be characterized by a predominance of unconjugated (free) bilirubin in the plasma. Severe hyperbilirubinemia is unlikely to occur with overproduction unless the excretory process is also impaired (1). The detachment of unconjugated bilirubin from albumin associated with uptake into the liver cell is an important step in excretion (1,2). The hepatic clearance of bilirubin from the plasma may be energy dependent (2). Following uptake, the liver cell processes the bilirubin and excretes it into the canaliculi as conjugated bilirubin (C. Bili.) (1). Cholestasis occurs when the excretory process or the passage of bile along the biliary system is interfered with (1,2,3,4). Cholestasis is generally characterized by increased plasma levels of C. Bili, total cholesterol (Chol.) and alkaline phosphatase (Alk. P.) (3). Hyperbilirubinemia associated with fasting occurs in many species (2,5,6,7,8,9,10). The problem apparently is related to a decreased hepatic uptake of bilirubin rather than to overproduction or under excretion (2). In this situation, the increase in plasma bilirubin is almost entirely due to the unconjuguated fraction.

With the advent in 1979 of routine biochemical profiling on all animals admitted to the clinics of the Ontario Veterinary College (OVC), it became apparent that many sick cattle had varying degrees of hyperbilirubinemia. In this present study, clinical and laboratory data from sick cattle were examined retrospectively to determine the incidence of and, if possible, the reasons for the hyperbilirubinemia occurring in such animals. It was found that in most instances the hyperbilirubinemia was due to an increase in

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unconjugated bilirubin and was not associated with obvious liver disease.

MATERIALS AND METHODS

ANIMALS

The biochemical profiles done on 1279 sick cattle admitted to the Large Animal Clinic of the OVC over a 33 month period were examined. Based on the total bilirubin levels (T. Bili.) two groups of cattle were selected for a detailed study. Group 1 consisted of the 195 animals that had a T. Bili. of 17 μmol/L or greater. This group was placed into four T. Bili. ranges of 17-33, 34-50, 51-67 and 68-310 μmol/L (Table I). Group 2 consisted of 195 sick animals selected at random from the 892 cattle whose T. Bili. was between 0.0-9.0 μmol/L (Table I). Data from the 192 animals with a T. Bili. between 10.0-16.0 μmol/L were not examined (Table I). In the event that more than one profile was done on a particular animal, the data analyzed were that contained in the profile with the highest bilirubin.

Blood for hematological studies was collected into vacutainers containing ethylene diaminetetraacetic acid (Becton Dickinson and Co. Canada Ltd., 2464 South Sheridan Way, Clarkson, Ontario) and blood for biochemical analyses was collected into vacutainers without an anticoagulant. Hematocrit (Hct) was measured using a Coulter Counter Model S (Coulter Electronics, Mississauga, Ontario).

Wright's stained blood films were used to assess red cell immaturity.

BIOCHEMISTRY

The following seven tests were measured using an American Monitor KDA Biochemical Analyzer (American Monitor Corporation, P.O. Box 68505, Indianapolis, Indiana). The methods and reagents used were those recommended by the manufacturers.

Total bilirubin was done using a modification of the method of Jendrassik and Grof (11). Conjugated bilirubin was as described for the Monitor KDA direct bilirubin reagent system. Unconjugated bilirubin was the difference between T. Bili. and C. Bili. Total cholesterol was determined by an enzymatic method that used cholesterol ester hydrolase and cholesterol oxidase. Creatine kinase (CK) was based on the kinetic procedure described by Rosalki (12). Alkaline phosphatase was based on the kinetic procedure described by Bowers and McComb (13). Aspartate aminotransferase (ASAT) was done using a modification of the kinetic method described by Henry *et al* (14). Albumin (alb.) was determined using the specific binding of bromcresol green to albumin.

RECORDS

Clinical records were available for all animals in groups 1 and 2. From these the clinical assessment, diagnosis, treatment and ultimate disposition were obtained. Necropsy records with histological data were available for all animals in groups 1 and 2, that died or were killed.

The reference ranges used for cattle at the OVC are hematocrit 0.18-0.47 L/L, total, conjugated and unconjugated bilirubin 0-9, 0-5 and 0-5 μmol/L respectively. Cholesterol 2.0-8.3 mmol/L, albumin 29-39 g/L, alkaline phosphatase, aspartate aminotransferase and creatine kinase 0-320, 39-72 and 40-200 IU/L respectively.

RESULTS

The distribution of T. Bili. values from 1279 sick cattle is given in Table I. Eight hundred and ninety two values were within the reference range of 0-9 μmol/L, 192 were between 10-16 μmol/L, 139 were in the range 17-33 μmol/L, 33 were between 34-50 μmol/L, 11 were between 51-67 μmol/L and 12 had T. Bili. values between 68-310 μmol/L.

CLINICAL ASSESSMENT

Group 1 animals varied in age from one day to 14 years (Table III). The presenting diseases were varied, often multiple and most were seemingly unrelated to the hyperbilirubinemia. Liver disease was diagnosed in eight animals and in four of these jaundice was clinically apparent (Table II). The most frequently made diagnoses were pneumonia, peritonitis, metritis, mastitis, displaced abomasum, enteritis, ketosis and neonatal disease. The most commonly described clinical signs were anorexia and rumen hypofunction. One hundred and nine animals (56%) in group 1 either died or were killed.

Group 2 animals varied in age from one day to 11 years (Table III). Most

TABLE II. Cattle from Group 1 with Total Bilirubin Values of 69 μmol/L or Greater. The Corresponding Values for C. Bili., Alk. P. and Chol. are Given

T. Bili. (μmol/L)	C. Bili. (μmol/L)	Alk P (IU/L)	Chol. (mmol/L)
69	5.1	464	1.6
71	5	151	0.3
81	16	196	2.3
84	22	237	1.2
91 A	19	781	1.3
93 A	16	217	1.5
101 A	9	770	2.8
114 A	36	858	3.0
145 AB	41	538	2.0
220 AB	131	737	3.5
277 AB	141	1353	5.4
310 AB	155	1298	4.4

A = Liver disease diagnosed
B = Jaundice clinically apparent

TABLE I. Distribution of Total Bilirubin Concentrations from 1279 Sick Cattle

T. Bili. Range (μmol/L)	Samples in Range (Total)	Samples in Range (%)
0-9	892	70
10-16	192	15
17-33	139	11
34-50	33	3
51-67	11	0.5
68-310	12	0.5

TABLE III. Relationship of Alk. P. to Age in Cattle with Normal T. Bili. (Group 2) and Cattle with Elevated T. Bili. (Group 1)

Age	Group 1 N	Group 1 Alk. P. IU/L Mean ± 2 S.D.	Group 2 N	Group 2 Alk. P. IU/L Mean ± 2 S.D.
1-14 days	36	636 ± 437	36	652 ± 699
15 days-12 weeks	11	365 ± 204	34	327 ± 198
13-51 weeks	11	333 ± 147	34	282 ± 162
1-3 years	40	244 ± 175	42	213 ± 126
4-7 years	59	282 ± 283	28	237 ± 362
8-14 years	38	240 ± 149	21	126 ± 99

of the diseases seen in animals in group 1 were also encountered in group 2. Neonatal disease occurred more frequently and in general the diseases seen were less severe in this group. Fifty-five animals (28%) in group 2 either died or were killed.

HEMATOLOGICAL RESULTS

For the animals in group 1 the range of Hct was 0.15-0.54 L/L. For group 2 the range was 0.10-0.60 L/L. Immature red blood cells were not a feature of the blood films examined from either group.

SERUM BIOCHEMICAL RESULTS

The relationship of T. Bili. to unconjugated bilirubin, C. Bili., Alk. P., Chol., ASAT, CK and Alb. is presented in Tables II and IV.

Unconjugated and Conjugated Bilirubin —The mean unconjugated bilirubin values for the T. Bili ranges of 17-33, 34-50, 51-67, and 68-310 μmol/L examined in group 1 were 21.5, 35.5, 49.8 and 88 μmol/L respectively. The corresponding mean values for C. Bili. were 1.9, 3.9, 6.7 and 50 μmol/L (Table IV). For the 12 cases in group 1 with a T. Bili. of 68 μmol/L or more the C. Bili. varied from 5.1-155 μmol/L (Table II). The mean unconjugated and C. Bili. values for the 195 animals in group 2 were 3.2 and 1.2 μmol/L respectively.

Alkaline Phosphatase — The mean Alk. P. values for the four T. Bili. ranges examined in group 1 were 285, 443, 313 and 639 IU/L respectively (Table IV). The mean Alk. P. value for the animals in group 2 was 287 IU/L. The Alk. P. varied with age being highest in young animals. For the 12 cases in group 1 with a T. Bili. of 68 μmol/L or more the mean Alk. P. was 633 IU/L and values varied from 151-1353 IU/L (Table II). The relationship of Alk. P. to age in groups 1 and 2 is presented in Table III.

Cholesterol — The mean Chol. values for the four T. Bili. ranges in group 1 were 1.6, 1.6, 1.6 and 2.8 mmol/L respectively (Table IV). For the 12 cases in group 1 with a T. Bili of 68 μmol/L or more the mean was 2.4 mmol/L and the Chol. values varied from 0.3 to 5.4 mmol/L (Table II). The mean Chol. for group 2 was 2.3 mmol/L (Table IV).

Aspartate Aminotransferase — The mean ASAT values for the four T. Bili. ranges in group 1 were 511, 505, 507 and 858 IU/L respectively. The mean ASAT value for group 2 was 171 IU/L (Table IV).

Creatine Kinase — The mean CK values for the four T. Bili. ranges in group 1 were 4740, 4930, 6043 and 12293 IU/L respectively. The mean CK value for group 2 was 1084 IU/L (Table IV).

Albumin — The mean Alb. values for the four T. Bili. ranges of group 1 were 25, 25, 28 and 30 g/L respectively. The mean Alb. value for group 2 was 29 g/L (Table IV).

DISCUSSION

This study indicates that hyperbilirubinemia is a rather common complication of disease in cattle. Visible jaundice occurs much less frequently and the hyperbilirubinemic state will often not be clinically apparent. Hyperbilirubinemia occurs in all age groups and is associated with a variety of diseases most of which are not considered to cause the retention of bilirubin. Most sick cattle with hyperbilirubinemia had varying degrees of anorexia and rumen stasis. A similar spectrum of disease was present in sick cattle with normal bilirubin levels but such animals tended to be less sick and anorexia was not as severe.

The severity of disease and mortality seemed to correlate with the degree of bilirubinemia. When serial serum bilirubin levels were determined on individuals over a period of days it was apparent that as the clinical condition deteriorated, the hyperbilirubinemia often increased: a decline in total bilirubin often but not always coincided with clinical improvement. This decline was at times very rapid with the T. Bili. returning to normal in 24-48 hours.

There was no obvious cause for the hyperbilirubinemia. Hemolytic anemia with overproduction of bilirubin was not a feature in any of the cases studied. Serum albumin levels were often low but this was likely a reflection of the primary disease and not related to the hyperbilirubinemia. Serum cholesterol which is frequently elevated in some species with cholestasis was, if anything, low in many cattle with hyperbilirubinemia. An increase in the serum levels of ASAT was a common finding in sick cattle both with and without hyperbilirubinemia. In almost all instances the increase in ASAT was concomitant with an increase in the serum levels of CK suggesting that the ASAT originated in muscle tissue rather than in the liver.

The distribution of total, unconjugated and conjugated bilirubin along with changes in the level of Alk. P. allowed those animals with hyperbilirubinemia to be placed roughly into one of two categories. In category 1, jaundice was not a clinical sign and the total bilirubin was usually less than 65 μmol/L. The increase in total bilirubin was predominantly due to

TABLE IV. Relationship of T. Bili. to Unconjugated Bili., C. Bili., Alk. P., Chol., ASAT, CK and Alb. in 195 Cattle with a T. Bili. of 0.0-9.0 μmol/L and 195 Cattle with a T. Bili. of 17-310 μmol/L

T. Bili. Range (μmol/L)	Unconj. Bili. Mean (μmol/L)	C. Bili. Mean (μmol/L)	Alk. P. Mean ± 2 SD (± U/L)	Chol. Mean ± 2 SD (mmol/L)	ASAT Mean ± 2 SD (IU/L)	CK Mean ± 2 SD (IU/L)	Alb. Mean ± 2 SD (g/L)
0.0-9.0	3.2	1.2	287 ± 275	2.3 ± 1.5	171 ± 730	1084 ± 4337	29 ± 4
17-33	21.5	1.9	285 ± 238	1.6 ± 0.7	511 ± 1299	4740 ± 15034	25 ± 5
34-50	35.5	3.9	456 ± 420	1.6 ± 0.5	505 ± 753	4930 ± 8451	25 ± 4
51-67	49.8	6.7	313 ± 282	1.6 ± 0.5	507 ± 483	6043 ± 11371	28 ± 3
68-310	88	50	639 ± 404	2.8 ± 1.4	858 ± 1814	12293 ± 36022	30 ± 6

changes in the unconjugated fraction with a much smaller increase in conjugated bilirubin. The serum Alk. P. was only moderately elevated. Approximately 90% of the animals with hyperbilirubinemia were in this category. The increase in unconjugated bilirubin with no indication of overproduction suggests that the hyperbilirubinemia may be related to a decrease in hepatic uptake of bilirubin such as is known to occur with fasting.

In category 2, jaundice and bilirubinuria may be a feature. The total bilirubin usually exceeded 65 μmol/L and the conjugated bilirubin, while not predominant, did contribute significantly to the increase. The level of Alk. P. was increased and this tended to parallel the increase in T. Bili. These changes suggest that cholestasis with some degree of liver damage was present.

While the hyperbilirubinemia occurring in many sick cattle may be related to failure at more than one stage of the excretory process, the inability of the liver to remove unconjugated bilirubin from the serum appears to predominate. This resembles the hyperbilirubinemia associated with fasting in sick horses (7,9). The hyperbilirubinemia seems to reflect the degree of, rather than the cause of, sickness and should not necessarily be attributed to liver disease or to excess bilirubin production.

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