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THE EFFECT OF GROWTH PROMOTANTS IN YOUNG GROWING HORSES

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Anabolic steroids are compounds that, when administered under certain circumstances, induce an increase in tissue protein from a given amount of digested protein (Vanderwal, 1976). Anabolic steroids have been used successfully as growth promotants in production animals and as therapeutic agents to treat debilitated animals including horses (O'Connor et al., 1973; Snow et al., 1982a). In the belief that certain types of athletic ability are related to muscle development, these anabolic steroids have been used to improve performance in humans and in horses (Ryan, 1976; Dawson and Gersten, 1978) Both steroidal and nonsteroidal compounds are suggested to be capable of producing such an effect. For several years testosterone and its derivatives have been extensively used in many countries in healthy racing animals or foals of all ages in the belief that athletic performance and muscle development are related in some equestrian disciplines (Snow et al., 1982b). However, there is generally a lack of scientific data to support this assumption (Snow et al., 1982a).

Early studies suggesting beneficial effects have not been supported by recent data. Stihl (1968) administered an anabolic steroid to a large group of horses in training. He found an improved appetite, increased body weight, and improved performance in geldings judged to have a weakness in performance. In the same study no beneficial effect could be found in stallions. Relying on an analysis of race results, a study by Dawson and Gersten (1978) claimed improved performance in Thoroughbreds of both sexes after treatment with boldenone undecyclenate.

In contrast Dietz et al. (1974) reported equivocal results in mature Standardbreds of both sexes and immature two-year-old Thoroughbreds treated with anabolic steroids. In a series of studies on healthy sedentary, mature, mixed breed geldings and a group of Thoroughbred geldings undergoing training, the investigators treated horses with weekly injections of nandrolene phenylproprionate. There was no effect of treatment on body weight, body measurements, hematological or serum biochemical variables, skeletal muscle composition, or metabolism that could be associated with improved racing performance (Snow et al., 1982a,b; Nimmo et al., 1982). However, of interest was that nitrogen excretion in treated animals was lower than in control animals during the first training period. There was no difference in the second training period. Weight loss occurred with training in

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both groups. These results suggest that under some circumstances, nandrolene phenylproprionate may have a protective effect on muscle breakdown, albeit mild.

Results of studies to date would suggest that there is a lack of scientific data indicating that anabolic steroids have any beneficial effects on otherwise normal, healthy horses. It might be construed from the information available that the steroidal anabolics may have a beneficial effect in debilitated animals or animals under stress, particularly associated with transition from stable to paddock or paddock to stable.

In the past 30 years there has been substantial interest in growth hormone (GH) or somatotropin (ST). Reviewing the literature there are over 42,000 references on this hormone between 1966 and 2000. There has been an exponential increase in literature from the mid 1980s when the synthetically produced hormone became available in humans. The commercial availability of recombinant equine somatotropin (eST) has only occurred in the past several years (registered in Australia in May 1998) and created considerable interest in the horse industry for its potential use in performance horses and foals. There is particular interest in treating dysmature foals or foals with early illness and adults with musculoskeletal injuries, wounds, and other performance-limiting diseases. However, it would be naive to ignore the significant interest in treating normal foals to enhance mature height, weight, and muscle bulk and to improve the ergogenic performance of young adult racing animals.

Growth hormone is a small protein produced by the anterior pituitary gland that is responsible for the growth of most body tissues. GH regulates growth through hypertrophy, hyperplasia, or both as a result of tissue differentiation, cell proliferation, and protein synthesis. It also has many specific metabolic effects including increasing the rate of protein synthesis, plasma insulin and glucose concentrations, fatty acid mobilization from adipose tissues, and the use of fatty acids as an energy source. It also decreases the rate of glucose utilization and influences fluid and electrolyte balance. GH is secreted in a pulsatile manner throughout life, declining with age. Stallions have greater frequency and amplitude of secretion, and concentrations are increased during acute exercise. The effects of GH can be mediated either directly through receptors in target tissues or indirectly through the production of somatomedins. The most widely studied somatomedin is somatomedin C or IGF-1 (Smith et al., 1999; Strobil and Thomas, 1996). IGF-1 is primarily produced in the liver but can be produced by a variety of tissues throughout the body. Administration of eST has been shown to increase the serum concentrations of IGF-1 in horses (Smith et al., 1999; Dart et al., 2003).

There has been considerable debate on the cross biological activity of different species forms of eST; it may be best referred to as species limited rather than species specific. Amino acid composition between eST, bovine ST (89.5%), and porcine ST (98.4%) shows considerable homology. Hence, there is some biological activity across these species. In contrast, homology between human ST and eST or bST is less than 67%, and neither bST nor eST is biologically active in humans.

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Furthermore, the potential for antibody production against analogous forms of ST used across species is high and potentially dangerous (Gerard, 2001).

eST comes as a sterile white powder, is made into a liquid by diluent, and is administered intramuscularly (EquigenTM, CSL Australia). The manufacturer's recommended dose regimen of eST is 10 µg/kg for 7 days followed by 20 µg/kg for 5 weeks. For the most part studies into the effects of eST have followed this or similar regimens.

The effects of eST administered at 20 µg/kg daily to four-month-old foals for a period of 12 months were evaluated (Capshaw et al., 2001; Kulinski et al., 2002). Treated foals were found to consume similar amounts of feed to controls, and there was no difference in body weight between the groups at any point in time. No difference in body measurements including height at withers, length, width of chest or rump, heart-girth circumference, length of head, or development of the limbs was detected between control and treated foals.

In these studies most organ weights were increased compared to controls, although in notable organs such as the heart these differences were not significant and all measurements were in the reference range for normal organ weights for horses. There were no gross pathological differences between the two groups, and of the tissues evaluated histologically, there were mild inflammatory changes observed in only a few tissues. The loin eye area at the tenth rib was significantly larger in treated animals, which is consistent with findings in pigs treated with pST (Evock et al., 1988). There were no significant hematological or serum biochemical differences between treated and control horses. However, treated horses did have an increased circulating glucose concentration and a tendency towards an increased serum insulin concentration. Increase in glucose and insulin concentrations had been documented in previous reports (Smith et al., 1999; Buonomo et al., 1996).

A biological effect of the injected eST in treated foals was confirmed by the persistent elevation in circulating IGF-1 concentrations compared to untreated foals. The greater response of control foals to challenge by the ST secretagogue compared to treated foals supported the activity. Despite this biological effect, daily treatment of eST at the recommended dose rate of 20 µg/kg failed to have an apparent effect on the growth and development of these foals.

The lack of an effect is somewhat surprising given the results in other species. Long-term treatment in short stature children with human ST increases height, albeit over several years (Sas et al., 1999; Radetti et al., 2000). Shorter term treatment in growing pigs with pST increases carcass length and bone mass (Evock-Clover et al., 1992; Klindt et al., 1992), while in beef cattle bST improves average daily gain, feed efficiency, and lean percentage of carcass, and reduces fat percentage by increasing plasma IGF-1 and enhancing protein synthesis (Schwarz, 1993). It is interesting to note, however, that treatment with pST in newborn pigs until weaning had no effect on plasma IGF-1 concentrations or growth performance (Dunshea et al., 1999).

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It is possible that an effect of eST on body characteristics would have been seen if the horses were GH deficient. Treatment of GH-deficient individuals with hST increased lean body mass, decreased body fat, and increased muscle mass (Bengtsson et al., 1993; Nelson, 1995). Alternatively, the dose of eST used in the present experiment may not have been sufficient to stimulate growth in these foals because many of the responses in growing pigs are dose responsive but not necessarily in a parallel fashion (Etherton and Bauman, 1998; Klindt et al., 1992). However, the IGF-1 concentrations in these foals almost doubled suggesting the dose was sufficient to elicit a response. In other studies in horses receiving similar doses, investigators noted elevated circulating leucocytes and subjective analysis of muscle definition but not ultrasound thickness of various muscle groups in aged mares (Malinowski et al., 1997), elevated IFG-1 concentrations in aged geldings and two-year-olds in race training (Smith et al., 1999; Julen Day et al., 1998), and enhanced follicular activity in anovulatory mares (Cochran et al., 1999a,b).

A group of researchers at Sydney University examined the effects of eST on yearling Standardbreds in training (Gerard, 2001; Lambeth, 2001). For 6 weeks Standardbreds received 10 µg/kg daily for 7 days and then 20 µg/kg daily for another 5 weeks while undergoing a 12-week treadmill-training program. The studies found there were small but statistically significant increases in average daily gain and body weight in treated horses compared to controls. The full weight of the gastrointestinal tract (GIT) expressed as a percentage of total body weight was greater in treated horses and probably reflected a greater dry matter intake in treated horses during the last 2 weeks of training. There were no effects on body height at the withers, organ weights, or digestibility of feed. The significant effects were small and considered to be of no consequence in terms of performance of young growing horses in training (Gerard, 2001). These findings were consistent with the previous studies in foals (Capshaw et al., 2001; Kulinski et al., 2002) and with studies in geriatric mares where there was no significant difference in body weight, body condition score, and dry matter intake between treated and untreated horses (Malinowski et al., 1997; Ralston et al., 1997).

There was no effect of eST on exercise capacity (Gerard, 2001). Maximum oxygen consumption, plasma lactate concentrations, heart rates, blood volumes, and run times to fatigue were not significantly different between treated and untreated horses (Gerard, 2001). These findings supported previous studies on aged, untrained geriatric mares that showed aerobic capacity was not improved after eST treatment (McKeever et al., 1998).

The yearlings treated with eST did develop significant decreases in PCV, Hb, MCH, albumin, CK, and AST and there was an increase in WCC, neutrophil, and platelet counts compared to controls. However, all variables remained within normal reference ranges suggesting any change would be of unlikely biological significance (Lambeth, 2001). Histochemical and biochemical analysis of weekly samples of the middle gluteal muscle was performed. There were no differences in muscle

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composition between eST-treated and control horses. At the completion of the study the weight of the semitendinosus and biceps femoris muscles in relation to body weight of eST-treated animals was compared to untreated controls. Treated horses had a significant increase in the weight of the semitendinosus but not biceps femoris muscle in relation to body weight. An increase in fiber size of the semitendinosus muscle could not be demonstrated in treated horses. Lambeth (2001) concluded there were no significant biological effects on skeletal muscle or hematological or serum biochemical variables associated with eST treatment in young training horses.

Gerard (2001) also evaluated the effect of eST on articular cartilage of the carpus and on the properties of the superficial flexor tendon in yearling horses undergoing training. Ex vivo proteoglycan metabolism of the harvested articular cartilage in treated animals was not different between treated and untreated horses. Biomechanical properties and concentrations of the matrix compound and cartilage oligomeric matrix protein were unchanged following treatment of horses with eST. These reports supported an earlier study finding no difference in the ex vivo biomechanical properties of normal superficial flexor tendons from adult horses treated with eST using the same dose regimen when compared with controls (Dowling et al., 2002a).

Cumulative evidence from these studies indicate that in the young exercising Standardbred horse administration of eST at the manufacturer's recommended dose does not have a major impact in terms of ergogenic augmentation. In addition, there may be limited prophylactic effects of eST on musculoskeletal tissues such as tendons and cartilage under high-intensity exercise. However, it remains possible that higher doses and/or a longer treatment period may have resulted in a different outcome. A study examining the safety margin of eST in the horse found that a single dose up to 5 times the recommended dose caused no untoward side effects (Dart et al., 1998).

Further studies have examined the potential therapeutic benefits of eST in the treatment of musculoskeletal injuries and in wound healing. Dart et al. (2002) examined the effect of eST on the healing of full thickness skin wounds on the distal limb in horses. The study found wounds on horses treated with eST retracted more during treatment and contracted faster after treatment stopped when compared to untreated horses. This is in contrast to a study looking at wounds on the pectoral region of horses where no difference in healing was found (Smith et al., 1999). The implication is that eST appears to modify wound healing of the distal limb. Further study is needed to evaluate whether there is any therapeutic benefit in specific wounds and whether there is potential benefit if eST were administered at strategic times during healing.

Dowling et al. (2002a,b) investigated the effect of eST on the in vitro healing of a tendon using a collagenase model of superficial flexor tendonitis. Tendonitis was induced by injecting the mid-metacarpal region of the tendon with 2000 IU of collagenase. Treatment consisted of eST at 10 µg/kg for 7 days followed by 20

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µg/kg for another 5 weeks. Following 6 weeks of treatment, horses were euthanized and tendons harvested for biomechanical testing. Tendons from treated horses had a significantly larger cross-sectional area and lower mean values for ultimate tensile stress and ultimate tensile strain. It was concluded that eST has a negative effect on the biomechanical properties in the early phases of healing superficial digital flexor tendons. Based on this model, eST cannot be recommended for treatment of superficial flexor tendonitis. In contrast a similar study looking at the effects of 10 intralesional injections of 2 µg of recombinant IGF-1 over a 20-day period on a collagenase-induced model of tendonitis in horses showed some biomechanical, cellular, and molecular improvement in healing eight weeks after induction of the lesion (Dahlgren et al., 2002). Other studies have suggested growth factors might modulate the repair process in damaged ligaments and tendons in a variety of species (Abrahamsson et al., 1991a,b; Abrahamsson and Lohmander, 1996; Des Rosiers et al., 1996; Murphy and Nixon, 1997). Given that it has been estimated that only 20-60% of horses sustaining superficial flexor tendonitis will return to racing and even then re-injury is common, further studies are required to evaluate the in vivo effects of growth factors on the ultimate healing and sustainable function under maximal exercise of flexor tendon lesions in the horse (Silver et al., 1983; Bramlage, 1986; Sawdon et al., 1996).

Finally the effect of eST on synovial joint metabolism has been evaluated. Using the manufacturer's recommended dose regimen, horses were treated for 6 weeks and synovial fluid was collected at 6, 8, 11, and 16 weeks. Cartilage was harvested at 16 weeks for analysis. Plasma IGF-1 and synovial fluid GH and IGF-1 were elevated in treated horses and compared to controls. Synovial fluid polysulphated glycosaminoglycans during treatment were significantly lower in treated horses. There was a trend for 3B3(-) epitope:GAG ratio to be higher in treated horses, although this difference was not significant. There was no difference in markers of cartilage metabolism between treated and untreated horses in the cartilage harvested at 12 weeks. The study suggests that eST can modify the joint environment and may achieve concentrations of IGF-1 within the joint used in joint resurfacing studies (Fortier et al., 1999). Further investigation into the role of GH in cartilage metabolism and repair are warranted (Dart et al., In press).

Studies into the role of the steroidal anabolics are limited; however, there appears to be little scientific evidence that there are anabolic effects that might be associated with increased performance of otherwise healthy animals or enhanced development of young horses. These drugs may have application in debilitated horses or in horses that are under stress, particularly in adjusting to the transition from paddock to stable or stable to paddock. It is important that these drugs do not become a treatment panacea, especially when horses may have underlying conditions.

Recombinant growth hormone is a relatively new therapeutic with demonstrated evidence of anabolic effects in a number of species. Recently, equine recombinant growth hormone has become available. To date studies examining the role of eST

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in the growth and development of foals and the effects of eST on young horses in work have been performed using the manufacturer's recommendations. Evidence would suggest that there is a biological effect when using the recommended dose. Contrary to the results of studies in other species, there appear to be no significant biological effects of eST on the growth and development of young horses. Similarly, there have been no credible effects on horses in training.

Studies looking at the potential therapeutic benefits of eST on the rehabilitation of horses with musculoskeletal injury or wounds are limited. Apart from unsubstantiated observations, there is no valid scientific evidence of a specific application to date. Evidence would suggest that eST may be able to modulate the joint environment. Further investigation of the role of eST in the prevention and healing of osteochondral lesions in the athletic horse may be warranted.

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