Abuse of recombinant human growth hormone: studies in two different dog models

A.E. Rigamonti, D. Scanniffio, S.M. Bonomo, S. G. Cella, A. Sartorio, E. E. Müller

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The search for inappropriately high growth hormone (GH) titers in plasma has been widely used to detect GH abuse, despite many shortcomings especially related to the pulsatile nature of GH secretion. Hence, the need for new anti-doping strategies. In the present study dogs were used to evaluate the ability of recombinant human GH (rhGH) to affect canine GH (cGH) release ensuing after somatostatin (SS) infusion withdrawal (SSIW) - a purported stimulus for the release of endogenous GH-releasing hormone (GHRH) - or the cGH response to administration of a GH-releasing peptide (GHRP): In the SSIW experiments, 8 beagle dogs of either gender (4-6 years old) were given a subcutaneus bolus injection of physiological saline (0.1 ml/kg) or, alternatively, rhGH (0.2 IU/kg s.c.) 60 min before the starting a continuous infusion of SS (4μg/kg g h i.v.) of 1.5 h duration. In the dogs given a saline bolus, SSIW was followed by a 'rebound' rise in plasma cGH levels. In contrast, in dogs which had received the bolus injection of rhGH, the cGH rise elicited by SSIW was completely abrogated. In the set of experiments with a GHRP challenge, 13 dogs of either gender (3-12 years old) received the following treatment schedule at least 15 days apart: (1) a single bolus injection of rhGH (0.2 IU/kg s.c.); (2) rhGH (0.05 IU/kg s.c.) daily for 12 days; (3) rhGH (0.2 IU/kg s.c.) on alternate days for 12 days, and (4) rhGH (0.2 IU/kg s.c.) daily for 12 days. For each treatment schedule, before treatment, during treatment (24h from the previous rhGH injection) and 1, 5 and 10 days after treatment, all dogs received an intravenous injection of a GHRP, EP51216 (125 μg/kg). In all treatments under baseline conditions, a single injection of EP51216 elicited an abrupt rise in plasma cGH. Twenty-four hours after the injection of an acute bolus of rhGH, the C_{max} and AUC_{0-90} of the GHRP-stimulated cGH response were significantly lower than the baseline cGH response. Five days later, there was a trend in the C_{max} and AUC_{0-90} towards complete restoration of the original values. One, 5 and 10 days after the end of the daily treatment with rhGH (0.05 IU/kg s.c.), no significant changes in the GHRP-stimulated cGH responses vs. the baseline GH response were recorded. In contrast, treatment with rhGH at a dose of 0.2 IU/kg s.c., on either alternate or daily administration, markedly reduced the GHRP-stimulated cGH responses evaluated after 3 and 5 rhGH injections. One day after the last rhGH injection, the EP51216-stimulated cGH response was still significantly reduced when compared with that present under baseline conditions. Five and 10 days following termination of rhGH treatment on alternate days, no significant differences in the C_{max} and AUC_{0-90} of the cGH responses to EP51216 were present. Differently, following the end of daily rhGH treatment, a marked inhibition in the C_{max} of the cGH response to EP51216 was still present at 1 and 5 days, though not at 10 days. In conclusion, these studies show that a single administration of rhGH can abrogate the cGH response ensuring SSIW or acute stimulation by a GHRP. The inhibitory effect of rhGH on the cGH response to GHRP is present even 5 days after termination of a short-lived treatment with rhGH at a dose (0.2 IU/kg) which, in the dog, is undoubtedly lower than that used in humans for doping purposes. Extrapolation of these preclinical results to humans may pave the way for the development of a new rhGH anti-doping test.